TUMOURS OF LYMPHOID TISSUE

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FOREWORD BY

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FOREWORD

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THIS monograph based on the study of 410 patients with tumours of lymphoid tissue is an important contribution to the present-day knowledge of this group of new growths Its importance lies chiefly in a clearer conception of the varieties or groups of these tumours and Dr Lumb succeeds in presenting a classification without confusing the already-confused nomenclature and by introducing only one new name Reticular Lymphoma On the other hand he discards many cumbersome and often misleading terms

Unlike other contributions on lymphoid tumours this book reads easily and presents the clinical and pathological features with simplicity The author makes out a good case for the rejection of the term Reticulosis as an overall label to cover a variety of tumours of lymphoid tissue origin as more or less a single entity He draws attention repeatedly to the histological and clinical changes which may occur in the same patient when lymph nodes are examined histologically at various stages throughout the course of the disease

There has been for many years some discussion and difference of opinion as to the nature of Hodgkin s disease This account leaves little doubt that the behaviour of this disease is that of cancer and that there is in fact no valid reason to consider it other than a malignant growth Dr Lumb postulates that the less common varieties the follicular lymphoma reticular lymphoma reticulosarcoma and reticulum cell sarcoma like the most common type Hodgkin s disease owe their variation in structure and degree of malignancy firstly to their cell type derivation and secondly to the amount of differentiation Such a concept is accepted in the case of tumours of epithelial and mesodermal origin and may equally well apply to those derived from lymphoid tissue

Those on whom falls the responsibility of the clinical management of patients will find this study of great practical help It is a guide to a more accurate prognosis and may influence the choice of treatment and so result in longer periods of survival The book therefore should be of value to the clinician be he physician radiotherapist or surgeon The pathologist will find it a clearly written essay on a highly specialised section of morbid histology For the student undergraduate and postgraduate it will prove a source of information which by its succinctness and clarity throws considerable light on one of the most difficult groups of malignant tumours

The book should remain for a long time a standard work on the pathology and natural history of tumours of lymphoid tissue

STANFORD CADE

TO
MY WIFE
JOAN

Printed in Great Britain

Photography has prepared the macroscopic photographs Mr E V Willmott at the Imperial Cancer Research Fund Laboratory at the Royal College of Surgeons of England prepared figures 1 9c and 1 11B and Dr David Tompsett of the Department of Anatomy at the Royal College of Surgeons painted the original for figure 1 9B Finally I must express my very sincere gratitude to my technical assistant Mr J R Stokes who has cut so many excellent sections and who has given me such great help with the preparation of the photomicrographs

GEORGE LUMB

London 1954

PREFACE

SINCE Hodgkin read his papers on Some Morbid Appearances of the Absorbent Glands and Spleen one hundred and twenty two years ago much has been written about those diseases which cause enlargement of lymph nodes liver and spleen and ultimately lead to death The reason which is given for adding to this literature now is the opportunity to present more than four hundred cases which have been studied carefully both by pathologist and clinician An attempt is made to show that it is possible on most occasions to make a reasonable estimate of the expected developments in any particular patient

The view is taken that the diseases to be discussed are true tumours showing varying degrees of malignancy This hypothesis may not be acceptable to all particularly as regards Hodgkin s Disease but it is felt that no satisfactory evidence is available in support of any other theory A particularly interesting group is that which is here called Reticular Lymphoma —a benign form of Hodgkin s Disease—which pursues a relatively benign course but in which most examples eventually merge into a malignant terminal phase Only tentative statements as to the details of this condition can be made at the present time but it seems certain that a relatively slowly advancing process which may remain latent for many years does exist Much more material must be collected in the future but the importance of being aware of such a disease pattern makes its discovery easier

Considerable care has been taken to present illustrations of good quality and to show as many examples as possible of the various appearances both of the tumours under discussion and of the diseases likely to cause difficulty in differential diagnosis Here my thanks must be given to my publishers Messrs E & S Livingstone Ltd for the great trouble they have taken in achieving good photographic reproductions

In the preparation of the accounts which follow many have been helpful but in particular my grateful thanks are due to Sir Stanford Cade Professor Geoffrey Hadfield and Professor R J V Pulvertaft who have given so much encouragement and advice To the members of the staff of Westminster Hospital and especially to Sir Stanford Cade Dr F M Allchin and Mr T M Prossor I am grateful for their wholehearted co-operation in allowing me to study cases under their care Dr K A Newton of the Department of Radiotherapy at Westminster Hospital has given me invaluable assistance in sifting material from clinical records To my pathological colleagues my thanks are primarily due to Drs G J Cunningham A D Morgan E Neumark and J W Whittick who have generously allowed me to study their material Dr Peter Hansell director of the Department of Medical

CHAPTER 1

STRUCTURE, FUNCTION AND SIGNIFICANCE OF LYMPHOID TISSUE

DESPITE the great advances in medical science made during the last quarter of a century any exact knowledge of the functions of lymphocytes lymphatics and aggregations of lymphoid tissue is still inadequate It is for this reason as much as any other that considerable confusion surrounds the classification and diagnosis of tumours arising in lymphoid tissue

It is necessary therefore before commencing any specialised account first to consider and analyse the existing views on anatomical and physiological factors in relation to this tissue

Anatomical Considerations

The lymphatic apparatus consists of a widespread network of vessels unorganised widely scattered collections of lymphocytes and lymph nodes This system wherever it is found is always closely associated with another group of cells of equally widespread distribution most frequently found lining sinuses but also scattered throughout the connective tissues of the body These cells are known as reticulum cells and are the functional cell component of the Reticulo-endothelial system of Aschoff For the purpose of the discussions which are to follow therefore lymphoid tissue will be taken to mean aggregations of lymphocytes with their supporting elements of reticulo-endothelial system wherever they are found in the body

The complexity of arrangement of the mammalian system wherein cells exist in the body in an environment different from that which surrounds the organisms outside seems to have made it necessary to provide a mechanism for clearing the tissues of substances not readily removed by the blood stream It is also certain that a physiological necessity exists for returning to the blood stream proteins which have leaked from capillaries

It is for this purpose that lymphatic channels exist and when the development of the lymphatic system is followed phylogenetically it is found that the structure reaches its greatest degree of complexity in the mammal Thus in the most primitive fishes there are no separate blood and lymph channels but in some venous lymphatics containing both blood and lymph are found As the phylogenetic scale is ascended creatures with lymph hearts are found which structures are capable of actively propelling lymph back into the circulation In birds lymph hearts disappear after embryonic life and valves

CONTENTS

Lymphoid Tissue and Lymph Nodes

Lymphoid tissue in mammals consists of a mass of free cells—the essential element of which is the lymphocyte—existing in a framework of reticulum cells capable both of supporting and phagocytic powers

Three groups of lymphoid tissue have been described by Ehrich (1929)

(1) Lymph nodes situated in the lymph stream

(2) Lymphatic tissue in mucous membranes with efferent vessels leading into the interior of the organism

(3) Lymphatic tissue in the spleen situated in the blood stream without any lymph vessel communication

To these groups Drinker and Yoffey (1941) have suggested the addition of a fourth

(4) Lymphatic tissue in bone marrow which occurs both in the form of nodules usually under pathological conditions and also as scattered lymphocytes

A fifth must be added

(5) Scattered lymphoid tissue in the lungs

The importance of lymphocytes in the fourth site centres around the unsolved problem of whether they arise there *de novo* to provide another area of lymphocyte production or whether the lymphocytes arrive there from the blood stream either to disappear or to mature

In connection with tumour formation the importance of the widespread nature of this system lies in the realisation that very diffuse or multifocal new growths are likely to occur

It has already been shown that the separation of lymphoid tissue from blood forming and myeloid tissue reaches its highest degree of development in the higher mammals but in the assessment of tumour formation which is to follow it is essential to remember not only the close association of these tissues to be found in a study of their embryology or phylogeny but also that the separation is by no means complete and that association becomes more apparent during disease Thus it has been stated that lymphoid tissue is to be found in bone marrow and it is also true that at times myeloid cells may be found in lymphoid tissue—the so-called myeloid metaplasia It is to be expected therefore that a very close association will exist between tumours arising from these tissues

The total quantity of lymphoid tissue in the human body is considerable and Drinker and Yoffey have estimated that in all it accounts for about 1 per cent of the body weight under physiological conditions In pathological states this figure would be increased enormously

It is usually accepted that in view of the almost identical appearances of lymphoid tissue wherever it is found it is reasonable to regard it as a single functioning unit For the purpose of tumour study therefore it is important to define the anatomical structure of a typical lymph node for not only is it representative of the system as a whole but it is the most common organ to

appear in the now completely separated lymphatic channels In this way lymph flow becomes dependant on chance muscular movements and varying pressures within the system The appearance of lymph nodes is found in some species of birds but they are only fully developed in mammals in which creatures valves in lymphatics are well defined

Thus it is seen that an essential change has taken place from a system where lymph is actively propelled by lymph hearts along valveless tubes to one where lymph flows along channels provided with valves in which are interspersed aggregations of lymphoid tissue known as lymph nodes where pooling of lymph in sinuses occurs Fluid movement in such a system is dependant on varying pressures and the efficiency of the valves

As the mammalian scale is ascended an increasing number of lymph nodes are found scattered along the route of flow and these nodes become relatively smaller in size In the pigeon for instance there are none whilst in swimming birds some are found—usually a pair in the cervico thoracic area and another pair in the abdomen In mammals lymph nodes increase in number so as to be present along each channel but whereas in the dog the cat and the rabbit the mesenteric lymph node for example tends to form one large mass—the pancreas of Aselli in the rhesus monkey and in man this organ disappears to be replaced by numerous scattered lymph nodes throughout the mesentery This is repeated throughout the body so that a definite tendency exists for an increase in total number of lymph nodes together with a decrease in individual size

Lymphatic Vessels

The origin of the lymphatic vessels is as yet not fully decided opinion varying between the view that they are new formations as opposed to the theory that they arise by budding from veins The exact nature of their origin does not seem to affect any of the physiological concepts concerned The most complicated system of lymphatics is found in man where they are distributed for the most part near the surfaces of the body—in the skin and mucous membranes Some difference of opinion exists as to the presence of lymphatics in muscle but most authorities describe them as running in the fascial planes around the muscles which by their contraction squeeze tissue fluids—ultimately to become lymph—into these channels

In other organs such as the spleen bone marrow liver lobules and pulmonary alveoli there is general agreement that no lymphatics exist and in these organs protein and tissue fluids escaping from the blood capillaries are returned into collecting lymph channels through specially formed sinusoids In the brain production and absorption of cerebro spinal fluid is so rapid as apparently to make lymphatics unnecessary

The lymphatic vessels are lined by flattened endothelial plates which are rarely if ever phagocytic and seem to possess no other function than that of retaining lymph

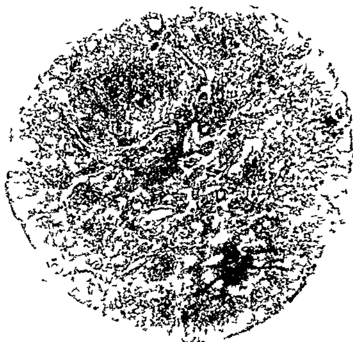


FIG 1 2
Small lymph node from neck showing general distribution of sinuses and lymphoid material (H and E × 0)

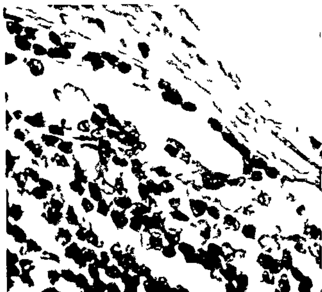


FIG 1 3
Peripheral sinus and capsule (H and E ×450)

be examined when an attempt is made to make a diagnosis of disease in lymphoid tissue

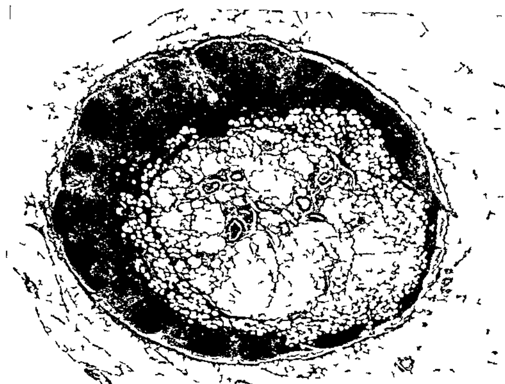


FIG 1 1

Small lymph node from axilla showing peripheral follicles and the tendency for the lymphatic tissue to be arranged around a central core of fat and vessels (H and E × ?0)

Structure of a Lymph Node

Most lymph nodes tend to be kidney shaped On cut surface in certain areas more particularly in the axillary and inguinal regions they may show themselves to be arranged around a central core of fat (Fig 1 1) They are enclosed in a firm capsule made up of fibrous tissue among the fibres of which occasional strands of smooth muscle may be demonstrated Contractility of the capsule has been suggested by Florey (1927) and Martin (1932) but this has been denied by Drinker and Yoffey Irregular strands of fibrous tissue pass from the capsule into the substance of the node

Perfusion of lymph nodes with India ink shows that lymphatic flow occurs by afferent lymphatics provided with valves into a cortical sinus (Figs 1 1 1 2 1 3) whence it passes through intermediate and medullary sinuses into the hilum and thence into the efferent lymphatic which emerges at this point The sinuses are lined partly by flattened endothelial cells of similar type to those lining lymphatic channels and partly by reticulum cells (littoral cells)



Fig 1 2
Small lymph node from neck showing general distribution of sinuses and lymphoid material (H and E [illegible]0)

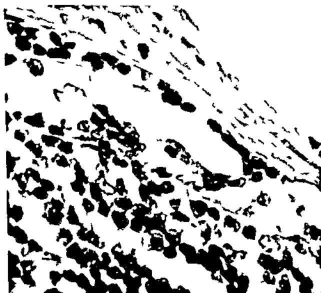


Fig 1 3
Peripheral sinus and capsule (H and E ×450)

capable of phagocytosis in situ or by becoming detached into the lymph stream (Figs 1 6 1 7) Between the sinuses are accumulations of lymphocytes either lying separately or in aggregations whilst among these aggregations still more compact masses (primary nodules) clumped around a central blood vessel can be seen (Fig 1 4) *In the primary nodule a more lightly staining* central area may sometimes be seen around which densely packed lympho cytes are arranged This appearance known as the secondary nodule or germinal centre was first described by Flemming (1885) who noted the large number of mitoses seen among the paler central cells and concluded that it was by the division of these cells that new lymphocytes are formed (Figs 1 4 1 5 1 6) That new lymphocytes can be produced without the presence of germinal centres is clearly seen in the large number of nodes where they do not exist and also before birth when the centres are not formed For these reasons therefore such authors as Hellman (1930 1939) have suggested that the germinal centres never occur in entirely normal lymph nodes but are the result of reaction to noxious stimuli

The lymphoid aggregations and sinuses are laid down on a diffuse trabeculated mesh of reticulum strands of which pass across the sinuses and on which are found the reticulum cells many of which can assume phagocytic powers and become detached from their basement membrane (Figs 1 6 1 7) These cells are identical with those found lining the sinuses and also with those scattered diffusely through the loose connective tissue of the body where they are known variously as clasmatocytes histiocytes and macro phages according to their function They would appear to be closely related to if not identical with the monocytes of the blood stream and bone marrow *Silver impregnation methods of staining outline the reticulum mesh and show* it to be diffusely spread through the lymph node except where lymphoid nodules or follicles occur and in these areas it is virtually absent (Fig 1 5) In association with some reticulum cells silver impregnated strands can be seen passing from one to another

Physiological and Functional Considerations

The functional aspects of lymphoid tissue still give rise to considerable controversial argument and some of the main considerations may briefly be *summarised as they occur in disease and in health*

Function and Significance in Disease

The principle function would appear to be associated with the body s defence mechanism in a manner which was first described by Virchow (1860) and which has since been referred to as the Barrier Theory *In his original* work it was shown that pus cells foreign material in the form of cinnabar used for tattooing and malignant cells could be removed from the lymph stream in the nodes

Drinker and *Yoffey have shown in numerous experiments* that the construction of the lymph node is ideal for filtration Numerous narrow



FIG 1 4
Peripheral follicles and adjacent sinuses
(H and E × 100)



FIG 1 5
The edge of a normal follicle showing relative absence of reticulin fibres in the central part
Reticulin impregnation × 100

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channels lead lymph under a definite head of pressure into wide sinuses from which large numbers of wide and irregular paths lead to the efferent vessel Flow is thus immediately slowed and pressure diminished The strands of reticulum stretching across the sinuses act as buffers further preventing flow and giving the phagocytic cells also of reticulum origin time to function In this way foreign particles such as red cells and bacteria are filtered with considerable efficiency The same is not true however of viruses and the work of McMaster and Kidd (1937) and of Yoffey *et al* (1939) seems to show quite conclusively that virus particles can pass through lymph nodes without being held up

The Barrier Theory of Virchow has more recently been investigated by McMaster and Hudack (1935) who have suggested that the lymph nodes function as :—

(1) Reaction centres

(2) Sites of antibody formation

Reaction Centres

Hellman (1921) Ehrlich (1929) and Hellman and White (1930) have suggested that the germ centres act as reaction centres for removing noxious substances both from the lymph and blood stream They have based this belief on the considerable increase in size and activity of germ centres following bacterial injections

An aspect of the barrier problem which is frequently overlooked has recently been emphasised by Menkin (1931 1938) An assessment of the defensive value of the lymphatic system must take into account not only lymph nodes and other lymphoid masses but also lymphatic channels Menkin s experiments in what he calls lymphatic blockade suggest that exclusion of organisms from lymphatic channels in bacterial inflammation is more desirable than their rapid transference along lymphatics to neighbouring lymph nodes

Antibody Formation

Pfeiffer and Marx (1898) were the first to show that a single injection of heat killed cholera vibrios into rabbits and guinea pigs was followed by an increase of specific antibodies in the spleen bone marrow and lymph nodes before there was any detectable change in the blood More recent work by McMaster and Hudack has lent support to a dual role of activity in defence for lymph nodes Firstly a filtration and reaction effect in eliminating noxious elements reaching them and secondly a role in antibody formation which are then poured into the blood stream to return to the site of inflammation McMaster and Kidd have suggested that the lymph nodes may be principally responsible for the immunity following Jennerian vaccination

It seems likely therefore that antibodies are produced in lymph nodes probably by the reticulum cell element There is no evidence that lymphocytes play any part in the production of agglutinins and other antibodies although

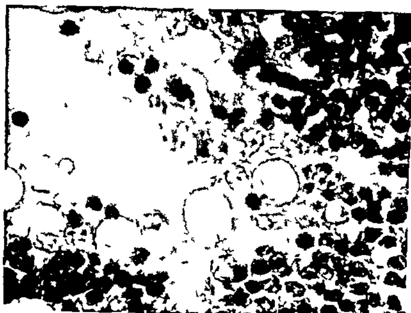


FIG 1 6
Lake of lymph in a normal sinus showing lymphocytes and reticulum cells (H and E ×450)

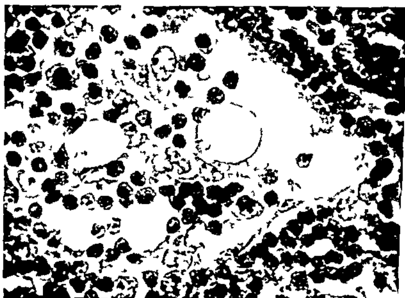


FIG 1 7
Contents of a normal sinus showing one cell in active mitosis (H and E ×450)

Lymphocytes may be formed —

(1) In the lymph nodes and lymphoid tissue of the alimentary canal
(2) In the spleen
(3) In the thymus
(4) In the bone marrow

In addition there may be scattered through the tissues small irregular collections of lymphocytes Cells formed in these areas may enter the blood stream *via* lymphatics and the thoracic duct In the case of the spleen certainly and possibly from the other tissues the passage may be direct

The thymus is quoted here as a site of origin for lymphocytes at least in early life as the view is accepted that small thymocytes and lymphocytes are identical

The details of the relationship between lymphocytes lymphoid tissue and the bone marrow is not known The question is whether lymphocytes enter the bone marrow from the lymphatics and if they do whether they disintegrate or act as stem cells in the production of other varieties of blood cells Another possibility is that some lymphocytes can be produced in the bone marrow later to be discharged directly into the blood stream as in the case of the spleen No final decision can be taken in this matter at the present time and for full details of the experimental work on the subject reference should be made to a specialised monograph such as that of Drinker and Yoffey

The fate of the lymphocytes in the body is an undecided problem and three main possibilities have been suggested —

(1) Disintegration in the blood
(2) Excretion into the lumen of the alimentary tract
(3) Passage into bone marrow

Experimental proof of disintegration of large numbers of lymphocytes in the blood stream or of considerable loss into the bowel is lacking whilst the problems associated with the bone marrow have been mentioned

The method of control of the balance between lymphocytes entering and leaving the blood stream is yet another question which has to be explained satisfactorily Many workers have postulated a hormonal control on the basis of clinical association between certain endocrine disorders and changes in the circulating lymphocytes Variations in acid base equilibrium and in blood pressure have also been invoked as possible causes The most important endocrine association seems to be the inhibitory effect exerted by the adrenal cortex on lymphoid tissue In Addison s disease there is usually a lymphocytosis and large numbers of lymphoid follicles may develop in the bone marrow Zwemer and Lyons (1928) found an increase in circulating lymphocytes in cats following adrenalectomy

Since the introduction of ACTH and cortisone it has been found that these substances have a remarkable effect on the haemopoietic system Considerable diminution of circulating lymphocytes has followed the introduction of these

it has been suggested that they may function in a carrying capacity by adsorbing the antibody on to their surface

Functions in Health

(1) Lymphocyte production
(2) Metabolism and transport of fat and of protein
(3) Vitamin storage
(4) Destruction of red cells
(5) Elaboration of internal secretion

The function of fat transport by lymphatics (lacteals) from the small intestine is well known and was described by the ancients The lymph nodes in the area during the passage of chyle show a cycle of changes (Dabelow 1930 31) The nodes become swollen and the reticulum cells particularly those in the sinuses become rich in fat some remaining *in situ* and others becoming detached as free macrophages The lymphocytes show no evidence of any participation in fat storage but following prolonged hunger a marked diminution in number of lymphocytes occurs

During prolonged malnutrition and starvation the changes in lymphoid tissue have been well described by Jackson (1925) who found generalised diminution in size of all lymph nodes and atrophy of lymphoid tissue The lymphoid nodules and cords in glands are more markedly affected than the stroma and reticulum cell elements

The striking reaction of hyperplasia and lymphocyte proliferation in lymphoid tissue as a result of foreign protein absorption is of particular interest in relation to allergic manifestations Not only is there an increase in total number of lymphocytes produced but they tend to be larger in size and to show markedly basophilic cytoplasm rich in mitochondria Longcope and Donhauser as long ago as 1908 showed that lymphocytes of large type contain proteolytic ferments

The significance of the vitamin content of lymphoid tissue is difficult to assess It is true that analysis of lymphoid tissue reveals the presence of all the known vitamins and that as a result of an insufficiency of A C or B complex lymphoid atrophy occurs whilst in rickets lymphoid hyperplasia occurs suggesting that vitamin D may have some inhibitory effect on lymphoid proliferation (Nitschke 1932)

The evidence for the suggestions which have been put forward that lymphoid tissue possesses an endocrine function seems to be quite inadequate (Drinker and Yoffey) Destruction of red cells by lymphoid tissue would seem to be a very minor function but inasmuch as reticulum cells with phagocytic powers are present in lymph nodes particularly this activity certainly can take place

The origin function and control of the lymphocyte is one which is as yet undecided with any degree of certainty The main points of argument may very briefly be stated as follows —

from 7 8μ in diameter showing similar cytological details to those described above These cells were thought to be only rarely motile a characteristic

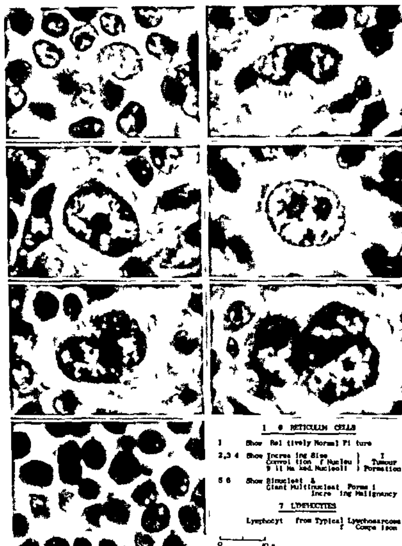


FIG 1 8
Composite figure to show varieties of reticulum cells as compared with lymphocytes (H and E ×450)

which has been used in their identification (Ehrlich and Lazarus 1905) but it must be made clear that it does not in any way provide a test as motility has been clearly established by numerous observers (Pulvertaft 1953)

substances in animals (Dougherty and White 1943) and similar results of a much more irregular nature have been reported in man

ACTH and cortisone have been used in the treatment of tumours of lymphoid tissue but as yet insufficient numbers are available to merit any dogmatic statement Early results in lymphosarcoma Hodgkin s disease and reticulum cell sarcoma seem to suggest that whilst temporary improvements are possible there is little evidence of there being any specific or prolonged effect on the course of the disease process itself (Copeman 1953)

The lymphocyte is an inconspicuous cell with no specific characteristic features and one for which despite repeated effort no specific function has been proved Many authors have felt that this apparent lack of function in a cell which is so universally found throughout the tissues suggests that it may be the precursor of many other varieties of cells into which it might be trans formed—for instance the myeloblast and the macrophage This school of thought believes that the large lymphocyte is a product of differentiation from the small and quotes the presence of mitochondria in the former as evidence of this

The opposite view which seems more reasonable to the writer suggests that the lymphocyte arises from a parent cell of primitive mesenchyme which also gives rise to many other cellular types—*i e* myelocytes granulocytes monocytes erythrocytes and reticulum cells or macrophages Its fully differ entiated form—the small lymphocyte—represents the adult stage of this particular type of cell variant This view therefore would indicate that the large lymphocyte is a less differentiated form and therefore a precursor of the small which is seen to be the exact opposite of what has been said above

The findings in tumours arising from lymphoid tissue seems to support the theory of origin of all these cells from a common parent variety for whilst it is possible to distinguish their fully differentiated forms by ordinary histo logical methods yet the larger the cells and the more undifferentiated they become from the point of view of tumour pathology the more their character istics merge until in the most anaplastic tumours it is impossible to identify them

In this connection again it is of note that the larger lymphocytes and so called lymphoblasts are to be found in the more rapidly progressive tumours whilst the small lymphocytes and therefore presumably those of greater differ entiation are to be found in the tumours of more benign potentiality

Before commencing an account of the specific tumour varieties it is necessary to describe some of the chief cytological characteristics of the lymphocyte and reticulum series of cells

The lymphocyte cell series exists in its most highly differentiated form which is a round cell measuring 4 5μ in diameter with a compact rim of basophilic cytoplasm and a well defined darkly staining nucleus containing scattered darkly staining chromatin and one or two small compact nucleoli (Figs 1 8 1 9a b) The more primitive lymphoblast is a larger cell varying

Other tests which have been suggested in the identification of lymphocytes are the demonstration of azurophil granules (Michaelis and Wolff 1902) Altmann-Schridde granules (Schridde 1907) the neutral red rosettes (Renaut and Dubreuil 1906 Simpson 1922) and the negative reaction to the oxidase test

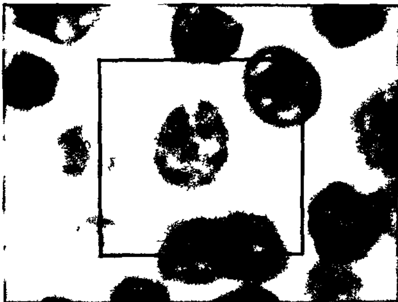
None of these methods is in any way specific and it must be admitted that the cytological characteristics of the fully developed cell still represent the best method of identification At this point mention must be made of the plasma cell which constitutes from 1 3 per cent of the haematopoietic



FIG 1 10
Plasma cells (myeloma cell) from sternal marrow (H and E × 1000)

cells in the normal human marrow (Maximow and Bloom 1952) and which is frequently found in serous membranes and in the lymphatic tissue It varies in size from one to three times that of a small lymphocyte and is capable of sluggish movement It is spherical in appearance and possesses well defined homogeneous deeply basophilic cytoplasm Characteristically there is a palely staining halo adjacent to the nucleus which structure is usually eccentrically placed and contains coarse darkly staining clumps of chromatin which are frequently best seen close to the nuclear membrane thus giving a clock face or cart wheel appearance (Fig 1 10) In most foci of plasma cells all transitions from small lymphocytes to plasma cells can be identified and some workers (Maximow and Bloom) claim to have observed the transformation of large lymphocytes to plasma cells in tissue culture It is fairly generally

A



B

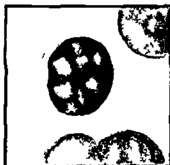
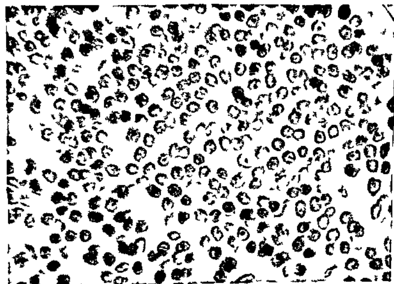


FIG 1 9

A and B Colour and black and white photographs of a typical lymphocyte as seen in lymphosarcoma (Fig 9A H and E ×1350 Fig 9B H and E ×1000)

C Typical lymphocytes as seen in lymphosarcoma (H and E ×700)

C



accepted that the lymphocyte may become a plasma cell (Drinker and Yoffey Jordan and Morton 1937) but the position cannot be accepted as fully proved for some workers such as Miller (1931) are emphatic in their assertion that no such association exists

From the point of view of routine histological diagnosis however the similarity between these cells both in structure and distribution is a striking feature and their appearance in most forms of the tumours of lymphoid tissue about to be described suggests a very close relationship between the two cell types

The reticulum cell series is seen in numerous forms It is a considerably larger cell than the lymphocyte measuring 12 16μ in diameter The cytoplasm stains palely with eosinophilic dyes and is irregular in quantity and outline Frequently prolongations are seen passing from one cell to another There is a single round oval or crescent shaped nucleus (8 × 9μ) the staining reaction of which is pale with a very well defined nuclear membrane and large rather diffuse markedly eosinophilic nucleoli In many of the tumours of lymphoid tissue binucleate and multinucleate forms are seen These are the cells described in the classical accounts of Sternberg (1898) and Reed (1902) and are correspondingly larger than the single nucleate forms sometimes reaching 30 35μ in diameter (*see* Figs 1 8 1 11a b)

It is believed that reticulum cells are identical with certain other cell types which have been given a variety of names by different observers These are the histiocytes clasmatocytes resting wandering cells and macrophages It is considered that these names represent merely variants of one type of cell—the reticulum cell—which is derived from primitive mesenchyme They have separate identity from lymphocytes and fibroblasts and are not developed from them Their distribution is widespread throughout the body where they occur as isolated cells in loose connective tissue and interspersed among the endothelial cells lining channels and spaces In response to various stimuli principally of an irritative nature they may proliferate to become actively motile and phagocytic but they cannot change their identity to produce lymphocytes



A



B

FIG 1 11

Colour and black and white photographs of reticulum cells in Hodgkin s Disease (Fig 1 11A H and E ×1000 Fig 1 11B H and E ×700)

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CHAPTER 2

HISTORICAL SURVEY

A HISTORICAL survey of our knowledge of primary tumours of lymphoid tissue must be traced from January 1832 when Thomas Hodgkin read two papers before the Medical and Chirurgical Society of London on some morbid appearances of the absorbent glands and the spleen The account which he gave seems to have made little impression on the medical thought of the time until Wilks in 1856 published his cases of Lardaceous disease and some allied affections At the end of his paper he refers to the fact that some of the cases he discusses had been described already in Hodgkin s earlier communication It was not however until 1865 in a further paper by Wilks that the position was somewhat clarified Here is found a review of the original cases of Hodgkin with a reassessment of the pathological material which was still available As a result of this work Wilks decided that four of the seven cases described by Hodgkin fell into a group which justified a separate title and formed a disease entity quite different from Lardaceous disease He also went on to describe a further eleven similar cases—making fifteen in all— where the glands were enormously enlarged and the spleen contained a white deposit like suet scattered through it Making generous tribute to its earlier discoverer he suggested that this process should be called Hodgkin s disease It is therefore of considerable interest to recall his original remarks and to note that nearly a hundred years later it is impossible to improve on them as a general description of the disease

It is an affection first observed by Dr Hodgkin who described it as a peculiar enlargement of the absorbent glands with a deposit in the spleen These are its main features although accompanied in life time by a remarkable anaemia and disposition to anasarca In the last few cases which I have observed the new adventitious material which has caused the enlargement of the glands and the deposit in the spleen has also been found in the liver and kidney and sometimes in the lungs It would appear then that this disease represents merely one mode in which an adventitious deposit can affect the organs and that it must take its place in the rank of malignant diseases or amongst those affections which are characterised by the development of new growths in the system The peculiarity of this affection still remains in the fact of the glandular system being especially affected and which gives rise therefore to peculiar symptoms This may be due to the lymphatic glands being first diseased for it has not yet been determined in this class of maladies how far the constitutional and how far the local causes predominate in causing the propagation of and in giving the character to new growth

Many observers through the years have studied again the seven cases described by Hodgkin and most have agreed with Wilks that only four of

them formed a group or entity (Horder 1932) although Fox (1926) felt that only three of the cases presented completely similar features Clearly speculations such as these are of historical interest only but most workers would agree with Naegeli s statement (1932) that Hodgkin in a masterly way and with astonishing clearness endeavoured to separate out the definite disease which we now know and all must admit that his was the first careful clinicopathological account of a tumour arising in lymphoid tissue

At about the time that Hodgkin was making his observations much research was going on into the diseases of lymphatic tissue but it was Virchow (1846) who gave the first adequate description of leukaemia and Cohnheim (1865) who described cases where similar changes occurred but where the number of abnormal cells appearing in the peripheral blood stream was not necessarily excessive

In 1863 Virchow described a malignant neoplasm affecting the lymphatic tissue under the title of lymphosarcoma This condition was more fully analysed by Dreschfeld in 1893 and Kundrat (1893) who also detailed many points of difference between lymphosarcoma and Hodgkin s disease These differences they based mainly on macroscopic appearances and spread of disease In the years which followed many histological accounts of these diseases appeared but the most important contribution was that of Sternberg (1898) who reported the microscopic appearances of Hodgkin s disease with great accuracy and concluded that the condition was a manifestation of tuberculosis Later Reed (1902) amplified the histology but felt that the association with tuberculosis was coincidental She did however consider Hodgkin s disease to be of inflammatory or granulomatous origin as opposed to the neoplastic nature of lymphosarcoma

The vast majority of workers accepted the viewpoint that a sharp line of demarcation could be drawn between these conditions until with further detailed study of the disease processes some investigators began to throw doubt on the concept Among the first of these were Benda (1904) and Yamasaki (1904) who showed in a small number of cases of Hodgkin s disease that capsular and venous invasion occurred which were considered to be features indicative of a malignant neoplasm Gibbons (1906) Coley (1907 1908 1915 and 1928) Dietrich (1908) Oliver (1913) Mallory (1914) Mueller (1920) McCartney (1928) Callender (1930) and Warthin (1931) all brought considerable evidence to bear over the years that lymphosarcoma and Hodgkin s disease were of common origin

In 1934 Ginsburg gave a good summary of the work indicating a neoplastic origin for these conditions and Warthin in a study of 506 cases of Hodgkin s disease aleukaemic and leukaemic lymphatic leukaemia and mycosis fungoides concluded that all these diseases are true blastomas differing only by degree of differentiation shown by cell types and site of origin

During this period many authorities still maintained the granulomatous origin of Hodgkin s disease Gordon (1932) stated that the morbid anatomy

and histology of lymphadenoma suggest that it is an example of an infective granuloma affecting the reticulo endothelial system The exact nature of the pathological agent that is present in lymphadenoma gland has not yet been determined there is a great probability that we are here dealing with an example of one of the larger viruses It is of interest to compare this statement of Gordon s with those of Coley (1907 and 1915) or Mallory (1914) who were equally convinced of the sarcomatous nature of the disease regarding it merely as a variety of round cell sarcoma

During the second and third decades of the present century it became clear to many observers that numerous varieties of disease existed within the broad limits of primary lymphadenopathies and attempts at classification were made Epstein (1925) and Puhr (1931) subdivided the conditions in a some what cumbersome manner based on function of the reticulo-endothelial systems In 1930 and again in 1932 Roulet introduced the term retothel sarcom which was quickly adopted under the title of reticulum cell sarcoma by pathologists all over the world as another group of lymph node tumours to add to the already recognised lymphosarcoma and Hodgkin s disease Con siderable difference of opinion has existed as to the nature of the cells in this type of tumour Ewing (1928) considered them to be immature lymphocytes derived from germinal follicles Medlar (1931) and Parker and Jackson (1939) regarded them as cells of the phagocytic series whilst Klemperer (1932 and 1934) felt that they were toti potential primitive mesenchymal cells

Pullinger (1932) in discussing the histogenesis of lymphadenoma improved the position considerably without actually suggesting any classification She based her beliefs on Maximow s (1927) theory of the multipotential capacities of that group of cells distributed as a matrix in lymphoid and myeloid tissue and in the splenic pulp In lymph nodes it also partly lines the sinuses in the marrow and spleen it lines the venous sinuses and appears as Kupffer cells again lining sinuses in the liver These cells are known as reticulum and are made up not of well defined units but of sponge like syncytia from which cells appear as a result of differentiation or degeneration Pullinger further clarified the title reticulo-endothelial system by pointing out the difference between reticulum and endothelial cells the latter according to Maximow being lining cells capable only of reproducing themselves Already many workers Andrewes (1902) Reed (1902) Longcope (1903) Kidd and Turnbull (1908) were convinced that proliferation of the reticulum cells together with the giant and multinucleated varieties which they produce was the essential feature of Hodgkin s disease Belief in the multipotential productivity of primitive mesenchymal cells together with suggestive histological and clinical data made it possible to group the leukaemias and sarcomatous conditions of lymphatic tissue together with lymphadenoma under a common heading and as a suitable title Pullinger suggested the term reticulosis which had already been introduced by Ewald (1923) and Letterer (1924) Ross (1933) suggested a classification based on Pullinger s observations but subdividing conditions into those with and without metabolic change—a somewhat artificial concept

Later Robb-Smith (1938) further modified the same viewpoint distinguishing reticulosis or hyperplastic conditions and reticulo sarcoma or true blastoma The former he divided into three main groups of disease arising respectively from undifferentiated cells in lymphoid follicles lymph sinuses and medullary pulp whilst the latter he subdivided according to cytological differentiation In this way all diseases affecting lympho-reticular tissue were grouped together Recently however observers have come to the view that interesting though this concept may be in theory it is of doubtful value in practical application The same observations may well be made of certain complicated clinical classifications (Callender 1934 Forkner 1937 1938)

In more recent years difference of opinion as to the nature of Hodgkin s disease has remained Such authors as Symmers (1948) believe in an inflammatory background possibly due to a virus and this observer speaks of a myeloidization of lymphatic tissue regarding the megakaryocyte as a cell of importance in this disease a view which is shared only by Medlar (1931) However the tendency is for more and more authorities to adopt the view that a group of primary tumours of lymphoid tissue exist varying considerably in degree of malignancy Warthin (1931) Gall and Mallory (1942) Herbut *et al* (1945) and Willis (1948) are but a few of the authorities who maintain that all these conditions are true blastomas

Such views fit the general concept of the theories of Maximow as modified by Pullinger but until more satisfactory evidence regarding the exact relationship of the primitive mesenchymal cell with its progeny is forthcoming it is impossible to be dogmatic However many pathological and clinical observations make it highly suggestive that a group of diseases exist which are conveniently studied together on the basis of common origin from a primitive mesenchymal stem cell

Such a group may be said to consist of two main varieties —

(1) Those where the disease is manifested by characteristic peripheral blood and bone marrow changes with or without hepatosplenomegaly

(2) Those where only rarely peripheral blood and bone marrow changes occur and where there is characteristically a lymphadenopathy with or without hepatosplenomegaly

It is clear that if the theory of a common parent cell is accepted then considerable overlap between these two groups would be expected to occur

The best example of this is the well recognised association between lymphatic leukaemia and lymphosarcoma often designated by the title of leukosarcoma Other examples which may be quoted are the occurrence of tumour masses (Chloromas) in some cases of myeloid leukaemia and the occasional occurrence of plasma cell leukaemia in multiple myelomatosis

There seems to be no doubt that multiple myelomatosis should be considered as an example of a tumour of the same basic origin as the leukaemias and tumours of lymphoid tissue The occurrence of soft tissue tumours lymph node involvement and leukaemia as well as widespread bone deposits

are well known in this condition (Lumb and Prossor 1948 Lumb 1952a) However the natural history of the disease makes its study more convenient in association with tumours of the bone and no further reference will be made to the condition

The close relationship of polycythaemia rubra vera with the leukaemias is also apparent and clearly this disease belongs to the same general group

This concept suggests therefore that a group of diseases exist in which examples are found of leukaemias rarely if ever associated with tumour masses and of primary tumours of lymphatic tissues rarely if ever associated with abnormal cells in the peripheral blood There are also examples where leukaemic blood pictures and tumour masses occur as closely associated variants of the same syndrome

Whilst bearing these facts in mind however it is still convenient to discuss the two groups separately as —

(1) Leukaemias including polycythaemia rubra vera

(2) Tumours of lymphoid tissue

It is with the second group that this communication is concerned primarily and only passing mention will be made henceforth of the leukaemias

CHAPTER 3

TERMINOLOGY AND CLASSIFICATION

SO far the term reticulosis has been avoided but it is now necessary to make clear what is meant by this word

Those who originally coined the term quite clearly meant it as a non specific all embracing title It should be used to indicate the reaction to varying stimuli of those mesenchymal cells large numbers of which persist into adult life in an immature fertile form capable of multipotential differentia tion These cells are found scattered diffusely throughout the body as well as being localised in certain well-defined sites such as the lymph nodes bone marrow liver and spleen

Thus inflammatory and degenerative changes just as much as factors of unknown aetiology including neoplasia will produce reactions in these cells The term reticulosis applied in this sense has value but it has no more specific significance than any other general pathological term In this way it is correct to speak of tuberculosis as an inflammatory reticulosis or of lymphatic or other leukaemia as a haemic reticulosis It is however a prostitution of the term to refer to a reticulosis or even worse to speak of one of the reticuloses for at once this implies a specific disease process with a clinical picture a prognosis and a histopathological pattern

It has already been shown how the aetiology of the disease group typified by Hodgkin s disease and lymphosarcoma has been and still is the subject of great controversy The principle difficulty lies in the decision as to whether these conditions are all tumours or whether some are proliferative lesions of granulomatous type The word reticulosis has come to be used very largely to describe this difficult group of diseases and in this sense it has no place for it then comes to indicate a specific clinico pathological entity as opposed to being a general term

Robb Smith (1938) has used the term reticulosis to mean a progressive hyperplasia of reticular tissue as opposed to reticulosarcoma which he used to indicate a true blastoma The criterion he employs for a reticulosarcoma is a proliferation of mesenchymal cells or their progeny which results in stromal destruction as well as infiltration

In his group reticulosis he includes various non specific and specific inflam matory conditions as well as Hodgkin s disease and lymphatic myeloid and monocytic leukaemia In his group reticulosarcoma one finds lymphosarcoma as well as a number of other subdivisions based on cytological type

Hodgkin s disease and the leukaemias on the one hand are thus divorced from lymphosarcoma a concept which cannot be supported as a result of study of the following series of cases

One cannot urge too strongly therefore that if the term reticulosis is to be used at all it should be as follows —

Reticulosis is an all embracing title indicating the reaction to varying stimuli of those mesenchymal cells found scattered throughout the body as well as being localised in certain well defined sites such as the lymph nodes bone marrow liver and spleen

It is considered important to realise the vast number of stimuli capable of producing changes in this widely dispersed cell system for then a more clear-cut appreciation of the clinico pathological varieties may be possible rather than the inevitable clouding which results from the use of a general non specific term in its wrong sense

It is proposed therefore to discard the term reticulosis as a descriptive title of the diseases under discussion here using it simply as a general patho logical term of the same nature and shade of meaning as fibrosis or gliosis They will be considered instead under the general heading of Tumours indicat ing a growth phenomenon superfluous to the requirements of the organism and purposeless growing in an unco-ordinated manner in relation to other cells and persisting after the stimuli which initiated their origin have ceased

The next task therefore is to attempt a classification of Primary Tumours of Lymphoid Tissue

CLASSIFICATION

It has been found satisfactory in classifying the leukaemias to make use of the blood cell type predominating in the particular tumour and in the same way it is felt that the proliferation along the line of the lymphocyte and the reticulum cell forms a convenient basis for analysing lymphoid tissue tumours

Thus certain broad groups might be defined where such differentiation has occurred *i e*

(1) Lymphocytic proliferation

(2) Reticulum cell proliferation

(3) Mixed cell proliferation where both lymphocytes and reticulum cells occur together with other cells formed from the primitive mesenchyme

Again within each of these groups a relatively well or poorly differentiated picture might be found and arguing along the lines of general histological experience applied to malignancy *a relatively bad prognosis might be expected* in the poorly-differentiated varieties as opposed to a relatively good prognosis in the better differentiated cases Further it must be added that it may be impossible to differentiate the more anaplastic types of one group from another and if finally one admits that close study of many areas of the same tumour may present differing histological appearances and that biopsies taken at different stages of the disease may not show a constant picture then one is left with a loose classification allowing for much overlap but indicating general principles of clinico pathological relationship along the same broad lines as the subdivision of carcinoma and sarcoma

Before approaching any exact account of individual tumours certain con cepts must be repeated and some form of classification made

These may be listed as follows —

(1) The conditions under discussion are considered to be true tumours of lymphatic tissue and to present an interrelated group fundamentally linked and merging with the leukaemias from which they are separated only for the sake of convenience of study

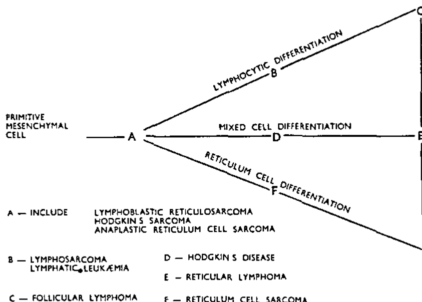


Fig 3 1
Histogenesis of tumours of lymphoid tissue

(2) All the cells found in these tumours arise initially from primitive mesenchyme and therefore considerable diversity of cell pattern is to be expected in view of its pluri potential capacity

(3) Although some of the tumours present a mixed cytological appearance defying clear nomenclature and leading to multiplicity of titles the majority have a well-defined histological pattern

(4) To these cases with constant clinico pathological features names may be given and it is proposed to retain titles already most commonly used

(5) It has been found of value to represent these views by means of a diagram in the form of a triangle (Lumb 1952b) (Fig 3 1) where poorly differentiated and often indistinguishable tumours are found at the apex and well-differentiated examples of the three major cytological variants are found towards the base It should be made clear that the better differentiated examples do not arise by transition from the more anaplastic varieties

(6) Most cases fall easily into one of the groups shown but a particular case may occur anywhere in the triangle During the course of the disease many cases show a tendency to anaplastic change or in other words a movement towards the apex of the triangle (Fig 3 2)

Assessing the above concepts it may be said therefore that individual tumours of lymphoid tissue present a pattern of cellular proliferation made up for the most part of cells of the lymphocyte series cells of the reticulum cell series and mixtures of these two

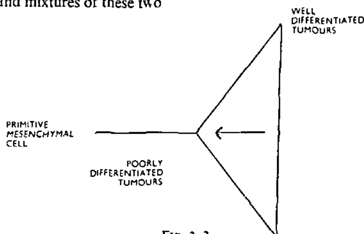


FIG 3 2
Histogenesis of tumours of lymphoid tissue

Thus among the tumours showing lymphocytic proliferation are found varying grades from those showing well marked differentiation with follicular proliferation to those made up of anaplastic cells of lymphoblast type Intermediate variants show every type of lymphoblastic and lymphocytic cell proliferation

Admixture of an occasional isolated reticulum cell among a majority of lymphocytes is found in the cases of reticular lymphoma and as the mixture of these two main cell types approaches 50 per cent of each so the classical *picture of Hodgkin s disease is produced merging in its turn into those cases* showing a polymorphic anaplastic cell mixture of the so-called Hodgkin s sarcoma type

Finally one finds examples of a pure reticulum cell proliferation of varying *degrees of anaplasia* with no evidence of abnormality of lymphocytes

It is proposed therefore to discuss the tumours of lymphoid tissue under the following titles

(1) THOSE SHOWING LYMPHOCYTIC DIFFERENTIATION

(*a*) *Lymphosarcoma* in which group are included those cases of lymphatic leukaemia which present as a lymphadenopathy

(*b*) Follicular lymphoma

(2) THOSE SHOWING RETICULUM CELL DIFFERENTIATION

(*a*) *Reticulum cell sarcoma*

(3) THOSE SHOWING A MIXTURE OF CELL TYPES

(a) Hodgkin s disease

(b) Reticular lymphoma

(4) THOSE SHOWING A DEGREE OF ANAPLASIA MAKING CELL TYPE DIFFERENTIATION IMPOSSIBLE

(a) Anaplastic sarcoma of lymphoid tissue In this group occur the anaplastic variants of the preceding sub-divisions and such titles as lymphoblastic reticulosarcoma and polymorphic or Hodgkin s sarcoma have been suggested These terms are not recommended as it is not considered possible to make a constant differentiation either from the histological or the prognostic standpoint

The following account is based on a study of patients treated at Westminster Hospital between 1940 and 1952 There are 410 cases where complete clinical records and adequate histological material are available In sixty-eight cases post mortem examinations were performed

One hundred and eight cases showed a proliferation of cells of lymphocyte type only and varied from the more benign follicular lymphoma where a high degree of differentiation is manifested by the formation of "pseudofollicles" in the tumour to the lymphosarcoma where follicular pattern disappears

Two hundred and eleven cases showed a mixture of cell types and included a gradation of clinico-pathological character varying from those with good prognosis where occasional isolated reticulum cells were scattered among sheets of lymphocytes (reticular lymphoma) to the varying mixtures of reticulum cells and lymphocytes including those examples where the reticulum cell together with its malignant giant multinucleate variants dominated the picture (Hodgkin s disease)

Twenty-one cases were found where the only cell type demonstrable was the reticulum cell (reticulum cell sarcoma) and seventy cases were classified as anaplastic sarcoma of lymphoid tissue These as their title suggests were all highly anaplastic tumours and it seemed unnecessary and often impossible to define the cells of origin as of lymphocytic or reticulum cell type These represented the apex or most undifferentiated point of the diagrammatic triangle

The varieties of tumours of lymphoid tissue seen at Westminster Hospital between 1940 and 1952 are shown in Table 1 Compared with other series the figures for Hodgkin s disease recorded here are rather high for instance Gall and Mallory (1942) classified 30 per cent. of their cases as Hodgkin s disease

Two reasons may be suggested to account for this difference The majority of these cases diagnosed by biopsy occurred in the younger age groups In Gall and Mallory s series a large number of autopsy cases were described and the group was drawn from a wider age range It may be assumed therefore that the cases here were younger and were seen at an

(6) Most cases fall easily into one of the groups shown but a particular case may occur anywhere in the triangle During the course of the disease many cases show a tendency to anaplastic change or in other words a move ment towards the apex of the triangle (Fig 3 2)

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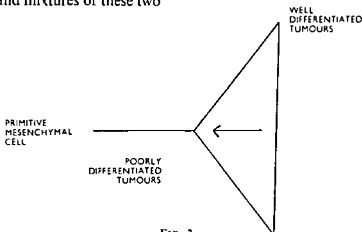


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(*b*) Follicular lymphoma

(2) THOSE SHOWING RETICULUM CELL DIFFERENTIATION

(*a*) Reticulum cell sarcoma

TABLE 2
SURVIVAL RATES

	No of Cases available for 5 Year Analysis seen up to 31/1 /47	No of Cases surviving 5 Years	Per centage surviving 5 Years	No of Cases available for 3 Year Analysis seen up to 31/1 /49	No of Cases surviving 3 Years	Per centage surviving 3 Years
Reticular Lymphoma	10	8	80 %	18	18	100
Follicular Lymphoma	8	5	62 5 %	18	13	72 22 %
Hodgkin s Disease	1 3	43	34 96	151	9	60·92 %
Lymphosarcoma over 35 years	?7	6	22 22 %	31	13	41 90 %
Lymphosarcoma under 35 years	8	1	12 50	1		16 66 %
Reticulum Cell Sarcoma	8	1	12 50	15	3	20
Anaplastic Sarcoma of Lymphoid Tissue	38	[illegible]	5 26	48	3	6 25
Survival irrespective of Type	[illegible]22	66	29 73 %	293	144	48 50

TABLE 3
SEX INCIDENCE OF TUMOURS OF LYMPHOID TISSUE

	Male	Female
Follicular Lymphoma	[illegible]	1
Lymphosarcoma	[illegible]2	1
Reticular Lymphoma	All Male	
Hodgkin s Disease	?6	1
Reticulum Cell Sarcoma	[illegible]	1
Anaplastic Sarcoma of Lymphoid Tissue	5	1

TABLE 1

VARIETIES OF TUMOURS OF LYMPHOID TISSUE

(*Westminster Hospital* 1940 1952)

	Cases		Cases
Follicular Lymphoma	29 = 7 1%	Lymphocytic Differentiation	108 = 26 3%
Lymphosarcoma	79 = 19 2%		
Reticular Lymphoma	21 = 5 1%	Mixed Cell Differentiation	211 = 51 2%
Hodgkin s Disease	190 = 46 1%		
Reticulum Cell Sarcoma	21 = 5 6%	Reticulum Cell Differentiation	21 = 5 6
Anaplastic Sarcoma of Lymphoid Tissue	70 = 16 9	Anaplastic Cell Variants of all Types	70 = 16 9%
Total	410 = 100%	**Total**	410 = 100%

earlier stage of the disease Both these conditions would lead to a higher percentage of Hodgkin s disease and a lower percentage of the anaplastic sarcoma group

It is interesting to note therefore that Gall and Mallory gave 20 per cent of their cases a diagnosis of lymphosarcoma as compared with 19 2 per cent in the present series

For the purpose of making an assessment of prognosis only the cases up to December 1947 (five year survivals) and December 1949 (three year survivals) have been analysed and these are grouped as follows —

	Cases up to 31st December 1947	*Cases up to 31st December 1949*
Follicular Lymphoma	8	18
Lymphosarcoma	35	43
Reticular Lymphoma	10	18
Hodgkin s Disease	1 3	151
Reticulum Cell Sarcoma	8	15
Anaplastic Sarcoma of Lymphoid Tissue	38	48
Total	[illegible]2	293

An analysis of presenting symptoms and primary sites of origin in the various tumours is given in Tables 6-18 Summaries of survival sex distribution and age incidence are given in Tables 2 3 4 5 and Figure 3 3

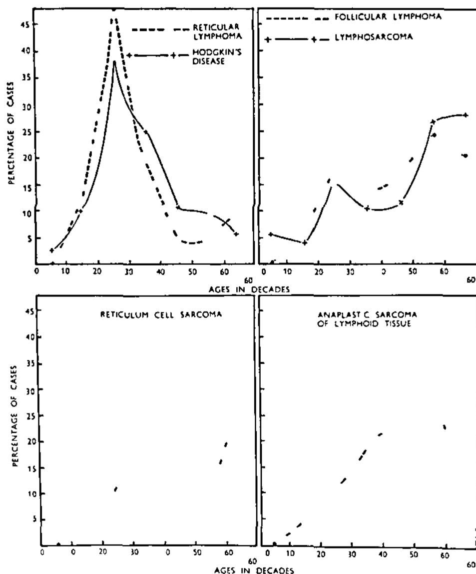


FIG 3 3
Graphs showing age incidence

TABLE 4

AGE INCIDENCE OF TUMOURS OF LYMPHOID TISSUE

1 IN DECADES

	Cases 1 10 Years	*Cases 10 20 Years*	*Cases 20 30 Years*	*Cases 30 40 Years*	*Cases 40 50 Years*	*Cases 50 60 Years*	*Cases Over 60 Years*
Follicular Lymphoma	0= 0%	2= 6 9%	5= 17 25%	4= 13 8%	5= 17 25%	7= 24 1%	6= 20 7
Lymphosarcoma	4= 5 1%	3= 3 8%	12= 15 2	8= 10 1%	9= 11 4%	21= 26 6%	22= 27 8%
Reticular Lymphoma	0= 0%	3= 14 3%	10= 47 6%	4= 19 0%	1= 4 8%	1= 4 8%	2= 9 5%
Hodgkin s Disease	4= 2 1%	19= 10 0%	74= 38 9%	46= 24 2	20= 10 5%	16= 8 4%	11= 5·9%
Reticulum Cell Sarcoma	0= 0%	1= 4 4%	3= 13 0%	5= 21 8%	3= 13 0%	3= 13 0	8= 34 8%
Anaplastic Sarcoma of Lymphoid Tissue	0= 0%	4= 5 7	8= 11 45%	14= 20 0%	16= 22 8%	18= 25 7%	10= 14 35%

Ages were analysed from the date of diagnosis of disease

TABLE 5

AGE INCIDENCE OF TUMOURS OF LYMPHOID TISSUE

2 IN THREE MAJOR GROUPS

	Cases Under 20 Years	*Cases 20 40 Years*	*Cases Over 50 Years*
Follicular Lymphoma	2= 6 9%	9=31·05%	13=44 8
Lymphosarcoma	7= 8 9%	20=25 3%	43=54 4
Reticular Lymphoma	3=14 3%	14=66·6%	3=14 3
Hodgkin s Disease	23=12 1%	120=63 1	27=14 2
Reticulum Cell Sarcoma	1= 4 4	8=34 8	11=47 8
Anaplastic Sarcoma of Lymphoid Tissue	4= 5 7	[illegible]=31 45	8=40

The ages given indicate the date when the disease was first diagnosed

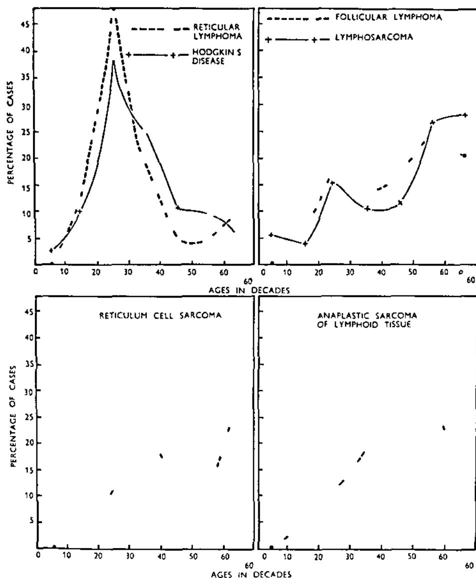


FIG 3 3
Graphs showing age incidence

CHAPTER 4

INCIDENCE OF TUMOURS OF LYMPHOID TISSUE

IN view of the considerable variation of opinion among different authors as to *terminology and aetiology in this group of conditions it is difficult* to give any very accurate picture of frequency of occurrence

Uddstromer (1934) writing on the occurrence of lymphogranulomatosis (Hodgkin s disease) in Sweden between 1915 and 1931 *gives a figure of 548* discovered cases or 0 054 cases per 10 000 living persons

Symmers (1924) found fourteen cases of Hodgkin s disease among 8 485 autopsies whilst Barron (1926) diagnosed as Hodgkin s disease twenty seven cases out of 7 253 autopsies

In an attempt to make a generalisation Jackson and Parker (1947) estimated that 0 25 per cent of deaths in a general hospital occurred as a result of Hodgkin s disease

Robb Smith (1947) has given incidence figures based on a six year survey in Oxfordshire and adding together those of his figures which are relevant to the diseases under discussion he gives an incidence per million of population of 47 5 cases of primary tumours of lymphoid tissue as against 36 3 cases of all leukaemias

In a recent survey of cancer in London made by the British Empire Cancer Campaign (Harnett 1952) ninety seven cases of lymphosarcoma including reticulum cell sarcoma are quoted This figure accounts for 0 7 per cent of all the cases of malignant disease reviewed No figure for Hodgkin s disease or any other tumour of lymphoid tissue is given

For the moment therefore until some uniformity of terminology exists in this group of tumours the only method by which any idea of incidence can be assessed is by the comparison of small personally recorded series of tumours of lymphoid tissue with other neoplasms where statistics are more accurate

Robb-Smith s figures suggest that the tumours of lymphoid tissue taken together occur slightly more frequently than the leukaemias whilst the British Empire Cancer Campaign figures show carcinoma of the breast to be twenty *times as common as lymphosarcoma and reticulum cell sarcoma*

For the purpose of comparison of this sort therefore the following figures have been extracted from the records of Westminster Hospital The figures given are small but it is felt that this disadvantage is outweighed by the fact that complete accuracy is assured

COMPARISON OF CASES OF CARCINOMA OF THE BREAST WITH PRIMARY TUMOURS OF LYMPHOID TISSUE AND LEUKAEMIAS SEEN AT WESTMINSTER HOSPITAL DURING 1950 1951 AND 1952

The figures given indicate new cases seen for the first time in the hospital

	1950		*1951*		*195[illegible]*		*Total*	
Carcinoma of Breast	132		138		154		4[illegible]4	
Primary Tumours of Lymphoid Tissue	36	5[illegible]	37	53	36	53	109	158
Leukaemias	16		16		17		49	

Thus during this three year period at Westminster Hospital cases of carcinoma of the breast have been 2 7 times as frequent as tumours of lymphoid tissue and leukaemias

CHAPTER 5

FOLLICULAR LYMPHOMA

(*Synonyms* Follicular lymphoblastoma
Giant follicular lymphoblastoma
Lymphoid follicular reticulosis)

FOLLICULAR lymphoma is a *condition the title of which is derived* from the histological appearance of the tumour tissue

The condition was originally described as giant lymph follicle hyper plasia by Brill Baehr and Rosenthal in 1925 who at that time considered it to be doubtful whether it represented a true tumour Later Baehr and Rosenthal in 1927 and Baehr in 1932 became convinced of its truly malignant nature Symmers (1927 1938 and 1942) has also given accurate accounts of this disease and whilst in his earlier work he was not satisfied as to its malignancy he subsequently stated that in its earlier stages it is a *comparatively innocent disease but it may undergo transformation into* a form of generalised sarcoma of lymph nodes Ewing (1928) and Jackson (1939) felt that it represented only a borderline manifestation of variable duration ultimately becoming one of the other forms of tumour of lymphoid tissue whilst Callender (1934) adopted an opposite view attributing to it a relatively high degree of malignancy

As a result of study of the cases in the Westminster Hospital series it is considered that it represents the best-differentiated variant in the group in which the lymphocyte is the type cell and that well marked follicle formation is characteristic Its prognosis compared with lymphosarcoma is good but during the course of the disease its pattern may become more anaplastic a change which is manifested by advancing malignancy

Incidence

Follicular lymphoma is a rare condition—twenty nine cases have been observed in the Westminster Hospital series or 7 1 per cent of the total number of tumours of lymphoid tissue analysed (Table 1) In Gall and Mallory s series (1942) forty two cases out of a total number of 618 (6 8 per cent) were classified as follicular lymphoma

Sex and Age Incidence

This disease shows a definite preponderance of cases among males In this series it occurred in the ratio of two males to one female (Table 3) There was an increasing incidence among patients in older age groups (Tables

Table 6

PRESENTING SYMPTOMS AND PRIMARY SITES OF DISEASE IN FOLLICULAR LYMPHOMA

27 Cases available for Analysis

Presenting Symptoms

1 Lump	22	= 81.5%
2 Tiredness	3	= 11.1%
3 Oedema Leg	1	= 3.7%
4 Dyspnoea	1	= 3.7%

Primary Site of Disease

LYMPH NODES		
Cervical	17	= 63%
Axillary	1	= 3.7%
Inguinal	4	= 14.8%
Mesenteric	1	= 3.7%
Occipital	1	= 3.7%
Submental	2	= 7.4%
OTHER SITES		
Spleen	1	= 3.7%

Table 7

SURVIVAL RATES IN FOLLICULAR LYMPHOMA

5 Year Survival

8 Cases available for 5 Year Analysis

Cases Less than 1 Year	*Cases 1-2 Years*	*Cases 2-3 Years*	*Cases 3-4 Years*	*Cases 4-5 Years*	*Cases More than 5 Years*
		1	2		5

= 62.5% 5 year survival

3 Year Survival

18 Cases available for 3 Year Analysis

Cases Less than 1 Year	*Cases 1 Year*	*Cases 3 Years*	*Cases More than 3 Years*
1	1	1	15

= 72.2% 3 year survival

4 5) thus 44 8 per cent of the cases occurred in people over fifty years and the most frequent decades affected were the sixth and seventh It is seen therefore that the age incidence in this condition corresponds closely to that in lymphosarcoma a feature clearly demonstrated by the curves of the graphs in Figure 3 3

Disease Distribution

Localised lymphoid swellings usually in the neck of elderly persons are recorded in this disease but the majority of cases have multiple glandular enlargements affecting most frequently the neck and retroperitoneal gland groups The spleen is palpable in 40 per cent of cases and may become very large (Case No 3) particularly in the terminal stages of the disease The lachrymal glands may be affected

Natural History of the Disease

The rare examples of localised lymph node enlargement may pursue an apparently completely benign course but in the majority of cases slow enlargement of lymph node masses with progression to widespread disease is the rule

Follicular lymphoma is regarded as a slowly advancing highly differentiated form of lymphosarcoma and as it progresses the clear-cut follicular pattern is lost as the histology becomes increasingly anaplastic (Figs 5 6 5 7 and 5 8)

The average duration of Gall and Mallory s cases was 5 6 years and in this series there were 72 2 per cent of three year survivals and 62 5 per cent of five year survivals

One of the features of the Westminster Hospital series was the absence of general signs and symptoms until the later stages of the disease It may be seen therefore that survival figures based on relatively small numbers of cases—an inevitable feature of a rare lesion—will tend to vary according to the stage at which the condition is first seen No characteristic blood or bone marrow changes have been observed in this disease There is usually no evidence of anaemia in the earlier stages but after a malignant course has supervened a moderate hypochromic anaemia may develop

Pathology

The affected lymph nodes are discrete and rubbery in consistency and may reach a considerable size On cut surface they are greyish in colour The spleen is fleshy on cut surface and shows multiple enlarged Malpighian corpuscles standing out as scattered greyish pin points (Figs 5 1 and 5 2) This feature may also be noticeable on the surface of lymph nodes whilst a follicular pattern is easily demonstrable when a stained microscopic preparation is viewed naked eye or with the aid of a hand lens (Fig 5 3)

Microscopically the characteristic picture is of large follicles of closely packed lymphoblasts and lymphocytes replacing the entire gland substance

and compressing the remaining normal structures Mitoses are infrequent The absence of reticulin in the follicles as compared with the relative increase in the surrounding compressed areas gives a highly characteristic appearance in silver impregnated preparations (Figs 5 4 5 5) The cellular make up of the follicles may show well marked central areas of pale cells surrounded by closely packed smaller lymphocytes Sometimes this mimicking of true germinal centres (pseudofollicles) is not so clear cut and cells of larger more primitive type are intermingled with the fully developed lymphocytes in an irregular manner The large follicles tend to split away from the rest of the material in microscopic preparations This is clearly an artefact and it occurs very frequently unless careful fixation methods are adopted (Figs 5 9 5 10)

As the disease progresses and anaplasia increases the clear-cut edges of the follicles begin to disappear a feature well demonstrated by silver impregation methods (Figs 5 6 5 7 5 8) and finally in the terminal stages a picture of anaplastic lymphoblastic proliferation is produced Sometimes occasional intermingled reticulum cells may appear and leukaemic changes of lymphocytic nature may supervene

Differential Diagnosis on Histological Grounds

It will be seen that this picture of follicular lymphoma bears a resemblance to the follicular hyperplasia which occurs as a result of inflammatory changes in lymph nodes The differences are as follows —

(1) The follicles in follicular lymphoma are large and closely packed They are newly formed and replace the entire gland structure In follicular hyperplasia the follicles are enlarged normal structures and are found principally around the periphery of the gland

(2) In follicular lymphoma mitoses are infrequent whereas in the inflammatory reaction they are common in the germinal centres

(3) Macrophages whilst common in follicular hyperplasia are not seen in the follicles of the tumour formation

(4) Sinuses are compressed and obliterated by the tumour whilst they are usually the site of reaction in inflammation

Cases seen for the first time after the anaplastic changes have commenced may pursue a short course and in these cases it seems reasonable to assume that the more benign stages have passed unnoticed A clinical picture of this type will be more marked when retroperitoneal glands are the main site of disease for in such a case no mass may be palpable until a late stage of the process is reached An example of this type of clinical picture is given in Case No 2

An illustrative case with long survival and few symptoms (Case No 1) is also described

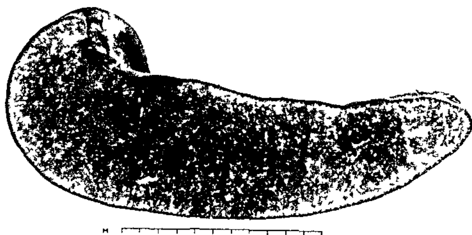


FIG 5 1
Cut surface of spleen removed at operation in a case of follicular lymphoma (Case No 3)

FIG 5 2
Magnified view of surface of spleen seen in Figure 5 1

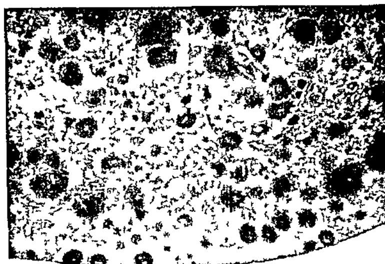


FIG 5 3
Lymph node showing diffuse pseudo follicles (H and E × 5)



FIG 5 4
Well demarcated follicles (H and E × 110)



FIG 5 5
Well demarcated follicles Reticulin impregnation (×450)



FIG 5 6
Disruption of follicle edges in malignant phase Reticulin impregnation (×450)

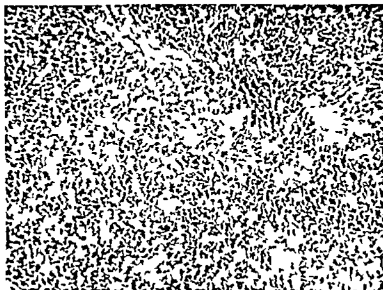


FIG 5 7



FIG 5 8

FIGS 5 7 and 5 8
Breakdown at edge of follicle to produce diffuse sheets of lymphocytes in increasing malignancy (H and E ×110)



FIG 5 9
Cracking producing pseudo follicles as a result of artefact
(H and E ×110)

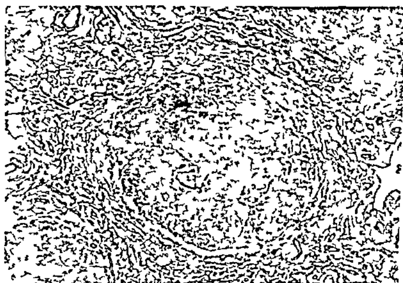


FIG 5 10
Reticulin impregnation of similar area to that shown in Fig 5 9 (×110)

CHAPTER 6

LYMPHOSARCOMA

(*Synonyms* Lymphocytoma and Lymphoblastoma)

LYMPHOSARCOMA first fully described by Kundrat in 1893 is a malignant tumour composed of lymphocytes and lymphoblasts It forms the link between the highly differentiated varieties of lymphocytic proliferation which produce follicles and the anaplastic tumours made up of lymphoblasts and primitive cells with numerous mitoses

Its association with lymphatic leukaemia is so close as to make it reasonable to assume that the two conditions represent different manifestations of a single disease entity Gall and Mallory (1942) found that 38 per cent of their cases which presented with tumours sooner or later developed a leukaemic blood picture In this series the figure has not been so high but 15 per cent of the cases have passed into a leukaemic phase This has been a common finding in the terminal state of the disease

It should be stressed that there are no differences in the tissue pathology of lymphosarcoma and lymphatic leukaemia other than the demonstrable presence of abnormal numbers of lymphocytes in the blood stream The disease distribution and natural history is the same and pieces of tissue examined histologically are identical in the two processes The importance of this point lies in the fact that a lymph node submitted for biopsy examination can be said to show lymphosarcoma only if it is known that the sternal marrow cytology and blood counts are normal

Incidence

Lymphosarcoma is one of the more common tumours of lymphoid tissue It accounts for 19 2 per cent of the Westminster Hospital series (Table 1) a figure in close agreement with that of Gall and Mallory who placed 20 per cent of their cases into this group

Sex and Age Incidence

A preponderance of males suffering from this disease is found in the ratio of 2 2 to 1 (Table 3) An increasing incidence is found among the older age groups in the same manner as follicular lymphoma (Tables 4 5 Fig 3 3) The resemblances between the curves of the graphs showing age incidence in these two conditions has already been noted Thus 54 4 per cent of the Westminster Hospital series were found in patients over fifty years whilst 8 9 per cent occurred in patients under twenty years The decades of life most frequently affected were the sixth and seventh



Fig 5 9
Cracking producing pseudo follicles as a result of artefact (H and E ×110)



Fig 5 10
Reticulin impregnation of similar area to that shown in Fig 5 9 (×110)

Examples are on record where an isolated focus of disease appears to be the only site affected This type of condition is sometimes seen in the gastro intestinal tract (Case 6) when an isolated area of lymphocytic infiltration in the wall of the bowel produces a tumour mass usually manifesting itself by obstructive phenomena (Figs 6 3 6 4 6 5 6 6)



FIG 6 1
Enlarged spleen in lymphosarcoma

Such a process must not be confused with intestinal involvement occurring as one focus of a diffuse lymphosarcomatosis in which case it is clear that excision would have no effect on the progress of the disease

Lesions of similar type occurring in the rectum have been described by Dukes and Bussey (1947) and two such cases have been seen at Westminster Hospital

Natural History of the Disease

Lymphosarcoma is a progressive malignant condition spreading widely to affect large areas of the body in the terminal stages

Much controversy has existed as to whether the widespread nature of the disease is the result of metastasis by blood or lymphatic stream or whether a multifocal origin would account for the multiplicity of sites of origin

It seems certain that both modes of proliferation occur Multifocal origin is to be expected in a disease thought to arise from primitive mesenchymal cells scattered diffusely throughout the body and in the early stages it is possible to demonstrate multiple foci which appear to arise simultaneously That true metastasis occurs is equally clear cut for invasion of veins and

TABLE 8

PRESENTING SYMPTOMS AND PRIMARY SITES OF DISEASE IN LYMPHOSARCOMA

75 Cases Available for Analysis

Presenting Symptoms		
1 Lump	47	= 62 7%
2 Tiredness	2	= 2 6%
3 Cough	5	= 6 7%
4 Pain	20	= 26 7%
5 Diarrhoea	1	= 1 3%
Primary Site of Disease		
LYMPH NODES		
Cervical	19	= 25 3%
Axillary	10	= 13 3%
Mediastinal	14	= 18 7%
Inguinal	1	= 1 3%
Aortic and Mesenteric	6	= 8 0%
Submaxillary	6	= 8 0%
Pre Auricular	3	= 4 0%
OTHER SITES		
Liver	1	= 1 3%
Tonsil	7	= 9 4%
Bowel	7	= 9 4%
Bone	1	= 1 3%

Disease Distribution

Lymphosarcoma manifests itself most commonly by lymph node enlarge ment in the neck mediastinum and abdomen In the cases studied at West minster Hospital no one particular area stands out as being the most frequent *site of origin thus the tonsil pharynx axillary and inguinal* lymph nodes have all been occasional initial sites (Table 8) In contradistinction to Hodgkin s disease the glands tend to produce massive swellings and consequent obstructive phenomena are common It may be for this reason therefore that all the cases with mediastinal involvement have had a bad prognosis The spleen is enlarged and diffusely infiltrated in one half of the cases seen (Fig 6 1) and in 25 per cent the bone marrow shows gross deposits of lymphocytic proliferation

As the disease progresses widespread involvement of many organs occurs among which the intestinal tract the kidneys and skin may be mentioned Skin infiltration produces one of the varieties of mycosis fungoides

Table 9
SURVIVAL RATES IN LYMPHOSARCOMA

5 Year Survival

35 Cases available for 5 Year Analysis

	Cases Less than 1 Year	*Cases 1–2 Years*	*Cases 2–3 Years*	*Cases 3–4 Years*	*Cases 4–5 Years*	*Cases More than 5 Years*
Over 35 Years	5	8	5		1	6
Under 35 Years	4	2		1		1
Total	9	10	5	3	1	7

= 22·22% 5 year survival over 35 years
= 12·5% 5 year survival under 35 years } = 17·36% average survival

3 Year Survival

43 Cases available for 3 Year Analysis

	Cases Less than 1 Year	*Cases 1–2 Years*	*Cases 2–3 Years*	*Cases More than 3 Years*
Over 35 Years	5	8	5	13
Under 35 Years	8	2		[illegible]
Total	13	10	5	15

= 41·90% 3 year survival over 35 years
= 16·66% 3 year survival under 35 years } = 34·28% average survival

lymphatics with subsequent deposition of disease in *numerous* organs is frequently demonstrable

The leukaemic changes which occur may be said to be nothing more than a blood stream transference of malignant cells

Inoculation of animals with transmissable lymphosarcoma and leukaemia has been shown by Furth *et al* (1933 1935) to produce widely infiltrating and invasive tumours similar to those seen in man and clearly spreading by metastasis



FIG 6 2
Diffuse infiltration of the wall of the heart in lymphosarcoma

The widespread nature of the spread of lymphosarcoma is a characteristic feature of the disease and in the terminal stages particularly the most extensive penetration occurs In this way tissue which may appear normal to the naked eye is found on microscopy to be infiltrated throughout its substance by lymphocytes

The metastatic sites are so numerous as to make it almost impossible to suggest that any of them show a preponderance At post mortem the organs most frequently affected other than the lymphoid structures are the kidneys lungs skin and bone marrow One site frequently affected is the heart (Fig 6 2) This is an interesting fact as it is such a rare site of metastasis in most

impregnation staining methods show only small fragments of reticulin substance remaining (Fig 6 15) The cells lie separate from each other with very scanty stroma Sometimes the sinuses are seen filled with lymphocytes (Fig 6 16)

Invasiveness is a characteristic feature of the condition and cells are seen penetrating into all the tissue spaces of an affected area Capsule penetration is common in lymph nodes with subsequent spread into surrounding tissues so that the edge of the lesion is usually ill defined

The more anaplastic forms of the disease are made up of larger lympho blasts and primitive cells which may in some respects resemble reticulum cells (Fig 6 17) These more anaplastic variants merge with the other ana plastic sarcomas of lymphoid tissue and become indistinguishable from them

Differential Diagnosis on Histological Grounds

The histological diagnosis of lymphosarcoma is usually quite straight forward for the complete obliteration of normal architecture by solid sheets of lymphocytes is characteristic In an individual instance of the more anaplastic type it may be difficult to decide whether to include the case under the diagnosis of lymphosarcoma or anaplastic sarcoma of lymphoid tissue If the concept of progressive anaplasia has been accepted however this problem is clearly one of an arbitrary nature and the histological description will indicate the degree of anaplasia It has already been made clear that the differentiation of lymphosarcoma from lymphatic leukaemia is impossible on purely histological grounds Sternal marrow and blood counts are essential

A case pursuing a typical clinical course is described in illustrative case No 4 (Figs 6 18 6 19)

other diseases One unusual site *noted in a post mortem on a child was* infiltration of the testis (Case 7)

The survival rate of lymphosarcoma is of some considerable interest The overall survival for more than five years in this group is 17 36 per cent as judged *by the cases at Westminster Hospital whilst 65 7 per cent* of cases were dead in less than three years However when the cases are studied according to age group a somewhat different picture is realised (Table 9) Thus in the cases under thirty five years of age 83 3 per cent were dead in less than three *years whilst only 12 5 per cent survived five years On the other hand* among the patients over thirty five years of age 22 2 per cent survived five years and 58 1 per cent died in less than three years It would appear therefore that there is evidence of increased malignancy among the younger people *suffering from lymphosarcoma This finding is in agreement with* those recorded in chronic lymphatic leukaemia (Windeyer and Stewart 1952)

When prognosis is studied in relationship to principal sites affected nothing clear cut emerges For the most part one finds a picture of progressive disease *unaffected by site involvement Two facts only are apparent Cases with* massive mediastinal involvement all pursued a rapid course In the series at Westminster Hospital among fourteen such cases representing 18 7 per cent of the total number studied only two survived a period of two years Study *of their case records seemed to suggest that the serious obstructive phenomena* produced by the disease at this site must play an important part in its rapid course (Case 5) (Figs 6 7 and 6 8) The other fact which has been mentioned already is that occasional examples are seen where the disease seems to be *confined to a single site as in those cases described in the bowel and in these* results are sometimes good following surgical excision of the involved area

No characteristic blood changes occur in lymphosarcoma although as the disease progresses a hypochromic anaemia is frequently found Mention *has already been made of the appearance of abnormal numbers of* lymphocytes in the peripheral blood so as to produce a leukaemic blood picture and in many cases examination of the sternal marrow reveals abnormal foci of lymphocytes and lymphoblasts

Pathology

The disease shows an essentially similar picture in all affected areas and is best described in terms of the lymphatic system

Lymph nodes are enlarged usually to a size varying from ½ cm to 2 cm in diameter but may become very large They tend to remain discrete and are rubbery in consistency usually somewhat softer than the affected glands in Hodgkin s disease (Fig 6 9) They are greyish in colour on cut surface and histologically show a complete replacement of the normal architecture of the tissue by sheets of lymphocytes *and lymphoblasts (Figs 6 10 14) The ratio* of one cell type to the other gives a good indication of anaplasia The most typical appearance is of a uniform mass of lymphocytes of the type described in a previous section with very small variation from one cell to another Silver



Fig 6 5
Diffuse infiltration of the stomach in lymphosarcoma



Fig 6 6
A further example of infiltration of wall of bowel by lymphocytes in lymphosarcoma (H and E × 5)

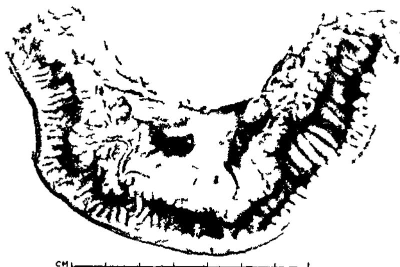


FIG 6 3
Localised area of infiltration of small bowel by lymphosarcoma (Case No 6)



FIG 6 4
Diffuse sheet of lymphocytes invading the wall of bowel (Case No 6) (H and E × 25)



FIG 6 9
Group of glands in lymphosarcoma removed from axilla



FIG 6 10
Section of lymph node showing replacement of normal archi tecture by a uniform sheet of cells (H and E × _)

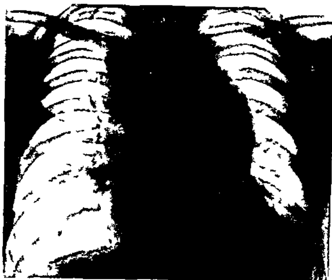


Fig 6 7
Radiograph of mediastinal mass in lymphosarcoma



Fig 6 8
Macroscopic appearance of mediastinal mass involving lymph nodes and lung



FIGS 6 13 6 14 and 6 15

FIG 6 13

Sheet of lymphocytes (H and E ×900)

FIG 6 14

Lymphocytes smeared from cut surface of lymph node in lymphosarcoma Papanicolaou stain (×900)

FIG 6 15

Relative absence of reticulin fibres Reticulin impregnation (×405)

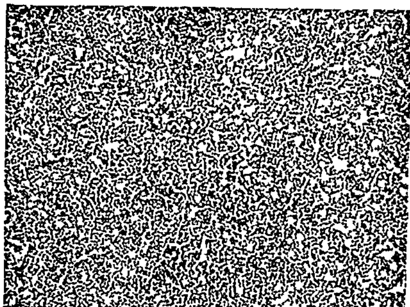


FIG 6 11
Lymph node showing a uniform sheet of lymphocytes (H and E × 110)

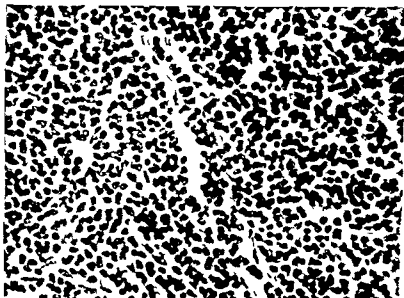


FIG 6 12
Uniform sheet of lymphocytes (H and E × 450)



FIGS 6 13 6 14 and 6 15

FIG 6 13

Sheet of lymphocytes (H and E ×900)

FIG 6 14

Lymphocytes smeared from cut surface of lymph node in lymphosarcoma Papanicolaou stain (×900)

FIG 6 15

Relative absence of reticulin fibres Reticulin impregnation (×405)

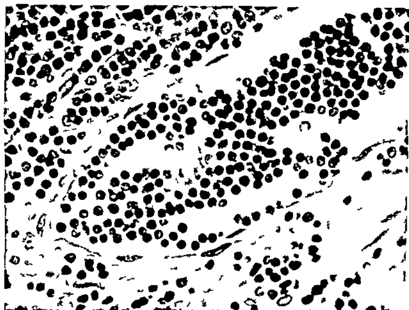


FIG 6 16
Lymphocytes lying in a small vessel at the edge of a lymph node in a case of leucosarcoma (H and E ×450)

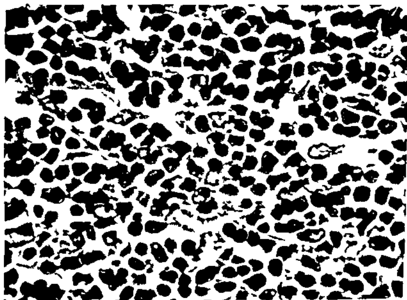


FIG 6 17
Sheet of moderately well differentiated lymphocytes and lymphoblasts in lymphosarcoma (H and E ×450)



FIG 6 18
Ulcerating tonsillar area in lymphosarcoma (Case No 4)



FIG 6 19
Healing lesion after irradiation therapy (Case No 4)

CHAPTER 7

RETICULAR LYMPHOMA

A BENIGN FORM OF HODGKIN'S DISEASE

(*Synonyms* Hodgkin s Paragranuloma
Lympho reticular medullary reticulosis
Early Hodgkin s disease
Benign Hodgkin s disease)

RETICULAR lymphoma is a disease process which has been recognised only recently Jackson in 1937 first drew attention to this condition when he reported a series of cases superficially resembling Hodgkin s disease but pursuing an unusually benign course He suggested the title of early Hodgkin s disease for this process but later Jackson and Parker (1944a b 1947) introduced the new name of Hodgkin s paragranuloma Robb Smith (1947) described an essentially similar entity which he called lympho reticular medullary reticulosis

It represents the most benign form of tumour of lymphoid tissue where both lymphocytes and reticulum cells proliferate together but it shows a tendency after some years to alter its clinico-pathological form becoming increasingly anaplastic

Incidence

Reticular lymphoma is a rare condition Twenty-one cases have been studied at Westminster Hospital which accounts for 5 1 per cent of the tumours of lymphoid tissue No other series can be quoted from the literature but Robb Smith states that lympho reticular medullary reticulosis has an incidence of 6 0 per million of the population and Bodley-Scott (1948) reports that for every six cases of Hodgkin s disease one case of lympho reticular medullary reticulosis is found

Sex and Age Incidence

This disease shows a male predominance and in the twenty-one cases personally seen all have occurred in males Jackson and Parker quote 73 per cent of their cases of Hodgkin s paragranuloma in males

The age incidence is very similar to that found in Hodgkin s disease thus 66 6 per cent of the cases occurred between the ages of twenty and forty years (Tables 4 5) and the graphs of age distribution of the two diseases show essentially similar curves (Fig 3 3)

Disease Distribution

The condition has been confined to lymph nodes in the cases examined in this series and the cervical glands have been the commonest site to be affected primarily (Table 10)

TABLE 10

PRESENTING SYMPTOMS AND PRIMARY SITES OF DISEASE IN RETICULAR LYMPHOMA

21 Cases Available for Analysis

Presenting Symptoms		
1 Lump	20	= 95 2%
2 Oedema Leg	1	= 4 8%
Primary Site of Disease		
LYMPH NODES		
Cervical	11	= 52 3%
Axillary	4	= 19 0%
Inguinal	3	= 14 4%
Submaxillary	2	= 9 5%
Mesenteric	1	= 4 8%
OTHER SITES		
Nil		

Natural History of the Disease

Reticular lymphoma usually commences as a localised affection of a group of cervical lymph nodes with little or no disturbance of general health The disease is only slowly progressive and may remain latent for many vears following diagnosis Jackson and Parker record a patient who has been well for thirty seven years since the condition arose although subsequent biopsies have shown the disease still to be present There is no example of such long duration at Westminster Hospital but one case has been followed for fifteen years before increasing malignant changes commenced (Case No 8) (Figs 7 12 15) and several cases are available for study where second biopsies showing similar changes to those in the original material have been performed after several years of completely normal health

Malignant change may occur as the disease progresses and Robb Smith has said that sarcomatous transformation may take place after an interval of ten to fifteen years This represents a useful generalisation but one case in the present series has undergone rapidly progressive change after only four and a half years It would appear that what was said earlier in relation to follicular lymphoma will probably equally apply in this condition Thus if several years pass before enlarged lymph nodes are noticed or if the gland group affected is in a site which is not readily detectable then clearly a period

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It represents the most benign form of tumour of lymphoid tissue where both lymphocytes and reticulum cells proliferate together but it shows a tendency after some years to alter its clinico pathological form becoming increasingly anaplastic

Incidence

Reticular lymphoma is a rare condition Twenty-one cases have been studied at Westminster Hospital which accounts for 5 1 per cent of the tumours of lymphoid tissue No other series can be quoted from the literature but Robb Smith states that lympho reticular medullary reticulosis has an incidence of 6 0 per million of the population and Bodley Scott (1948) reports that for every six cases of Hodgkin s disease one case of lympho reticular medullary reticulosis is found

Sex and Age Incidence

This disease shows a male predominance and in the twenty-one cases personally seen all have occurred in males Jackson and Parker quote 73 per cent of their cases of Hodgkin s paragranuloma in males

The age incidence is very similar to that found in Hodgkin s disease thus 66 6 per cent of the cases occurred between the ages of twenty and forty years (Tables 4 5) and the graphs of age distribution of the two diseases show essentially similar curves (Fig 3 3)

cent of cases living more than five years and no cases dying in less than three years Of the two cases which have died in less than five years one died three and a half years after diagnosis with an apparently unrelated carcinoma of the rectum In the other case rapid dissemination occurred after four and a half years as has been mentioned already

When advancing malignant changes occur during the later stages of the disease widespread tissue involvement occurs and the condition assumes the picture seen in a case of rapidly deteriorating Hodgkin s disease

No characteristic blood or bone marrow changes occur in this disease until in those cases where a more malignant phase supervenes blood pictures resembling those seen in Hodgkin s disease (p 78) may be observed

Pathology

The affected glands are enlarged but not to a very great size so that the nodes examined in this series have measured 2 3 cm in their longest diameter They tend to remain discrete and are rubbery in consistency of much the same type as Hodgkin s disease being firmer than the glands of lympho sarcoma On cut surface they are greyish in colour and show no tendency to necrosis or haemorrhagic degeneration

Microscopically the normal architecture of the lymph node is replaced by a proliferation almost entirely composed of mature lymphocytes among which are scattered occasional reticulum cells One of the characteristic features is that the reticulum cells remain isolated and do not tend to occur in clumps (Figs 7 1 11) The reticulum cells although relatively few in number as compared with Hodgkin s disease are a clearly recognisable feature of the histological pattern and are easily identified at low magnifications They possess the characteristic features of large well-defined nucleus with prominent eosinophilic nucleolus and irregular palely eosinophilic cytoplasm Binucleate forms have been seen but multinucleate giant cells are not common Mitoses have not been observed Occasional eosinophils and plasma cells have been seen but are not a characteristic feature of the cytology There is no tendency for capsule invasion or necrosis to occur In the cases examined in this series fibrous capsular thickening has been a frequent occurrence and collagen strands passing through the structure of the node have caused irregular lobulation frequently recognisable by a naked eye or hand lens examination of the section Particular attention has been paid to this feature in an account by Harrison (1952) (Fig 7 1)

When more malignant changes supervene an increase in the number of proliferating reticulum cells is seen so that the histological picture comes more to resemble a typical Hodgkin s disease or in the final stages an ana plastic sarcoma of lymphoid tissue

Illustrative case No 8 is a good example of a case which was followed through the whole range of change from a relatively benign lesion with no general ill health which continued for ten to fifteen years followed by a

of shorter duration will elapse between the patient s first visit for advice and the subsequent malignant change In this connection two patients seen recently may be quoted In one a lymph node showing the changes of reticular lymphoma was removed from the neck in February 1947 after its discovery at a routine medical examination The patient has at no time experienced any ill health and now six years later although he himself has no complaints a firm spleen enlarged three finger breadths below the costal margin has been discovered at another routine examination From the second patient a lymph node showing the changes of reticular lymphoma was removed from the neck in November 1944 and a second biopsy in December 1952 showed essentially

TABLE 11

SURVIVAL RATES IN

RETICULAR LYMPHOMA

5 Year Survival

10 Cases available for 5 Year Analysis

Cases Less than 1 Year	*Cases 1 - Year*	*Cases 2 3 Years*	*Cases 3 4 Years*	*Cases 4 5 Years*	*Cases More than 5 Years*
			1	1	8

= 80% 5 year survival

3 Year Survival

18 Cases available for 3 Year Analysis

Cases Less than 1 Year	*Cases 1 - Years*	*Cases - 3 Years*	*Cases More than 3 Years*
			18

= 100% 3 year survival

similar appearances More recently however he has returned showing for the first time signs of general ill health and with enlarged lymph nodes in many areas But for chance findings at routine medical examinations neither of these patients would have been recognised as having any abnormality The first man still insists that he enjoys perfect health whilst the second would have reported sick only within the last few weeks

Peters (1950) suggests that a better prognosis is found in this condition as compared with Hodgkin s disease largely because only one group of lymph nodes is affected at the time the disease presents itself

The survival rates of the cases of reticular lymphoma have been the best of the various types of tumours of lymphoid tissue (Table 11) with 80 per

more material must be collected before any truly dogmatic statement can be made about it

Criticism against the diagnosis can be levelled from two points of view First of all if a patient lives for a long period of time in good health and without any recurrence of lymphadenopathy after the diagnosis has been made doubt may arise as to whether anything more than some non specific inflammatory change has caused the lymphadenopathy Secondly it may be argued that if malignancy can supervene in a period of time which cannot be assessed accurately then there is little value in making a new subdivision

It must be admitted that the majority of cases to which a diagnosis of reticular lymphoma is applied are made in retrospect—that is by careful assessment of cases diagnosed as Hodgkin s disease which have progressed more favourably than might have been expected It is also clear that for some time to come new cases will largely be discovered in this way

Most will agree however that in the experience of all those interested in tumours of lymphoid tissue are to be found cases diagnosed as Hodgkin s disease where there is no doubt that a gross abnormality of lymphoid tissue exists yet where symptom free survival for many years has occurred Reassessment of such cases does reveal what appears to be an apparent clinico pathological entity

With the information available at the present time and based particularly on the material of this series it is felt that a disease group exists showing features somewhat similar to Hodgkin s disease but where symptom free survival is very much more prolonged Its identification seems justified along the lines laid down and careful reassessment of patients originally diagnosed as Hodgkin s disease yet who have followed a long and symptom free course seems a profitable way of discovering new cases and adding to our knowledge of the condition

It must be stressed however that only by a careful collection and assessment of cases of this type can any final decision be made and that for the moment any description such as the one given above must be regarded as of a tentative nature

Two cases following long courses are described in illustrative cases Nos 8 and 9

period of two to three years when the picture of Hodgkin s disease was simulated and the condition advanced more rapidly with finally a short terminal period of rapid malignancy of the type seen in a case of anaplastic sarcoma of lymphoid tissue (Figs 7 12 15)

Harrison has suggested that if the condition ultimately assumes malignant form there is little value in making the diagnosis but in his series of cases no malignant change had supervened One cannot entirely agree with this concept for it seems reasonable to identify a condition by name which is likely to pursue a favourable course even if it is realised that after a period of time advancing malignancy may supervene

The title for this condition gives rise to some difficulty Jackson and Parker (1944a b c 1947) have used the term Hodgkin s paragranuloma because of its close resemblance to Hodgkin s disease which they term Hodgkin s granuloma They consider the condition to be of inflammatory origin and they feel it is not improbable that the paragranulomatous form bears to the granulomatous type of the disease the same relation that a primary tubercle does to fibrocaseous tuberculosis

It is felt that this concept is essentially incorrect and that the disease provides another example of a tumour which may remain benign for a long period yet which at all times is potentially malignant Robb Smith s title lympho reticular medullary reticulosis is admirable in that it describes the cell types found in the tumour However the name is very cumbersome and it is felt that the concept of a medullary reticulosis as has already been indicated is an artificial subdivision Unfortunately therefore it seems necessary to introduce a new term for although it is felt that this condition represents a benign form of Hodgkin s disease it seems unsatisfactory to modify a title where a man s name is involved by adding qualifying terms

As a suitable alternative reticular lymphoma is suggested as this fits in with the general scheme of terminology and at the same time indicates the principle diagnostic feature of the histological pattern—namely the replacement of normal architecture by a proliferation of lymphocytes among which are found scattered reticulum cells

Differential Diagnosis on Histological Grounds

Diagnosis of reticular lymphoma is of some importance for although it is a rare condition it will most often be found in a patient who is apparently in excellent health The decision will usually rest between the exclusion of a chronic inflammatory condition with fibrosis on the one hand and true Hodgkin s disease on the other Destruction of normal architecture by the type of cellular proliferation already described must serve to differentiate the inflammatory states where distortion may result from sinus proliferation The relatively small number of scattered reticulum cells together with the patchy fibrosis should distinguish it from Hodgkin s disease

A relatively dogmatic account of this disease process has been given above in order to establish its outlines It should be made clear however that much

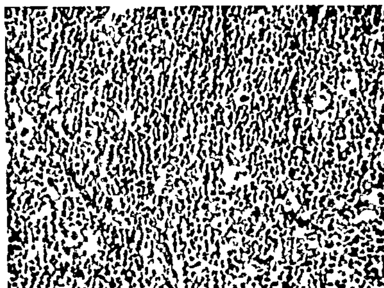


FIG 7 3
Lymphocytes interspersed with isolated reticulum cells (H and E 175)

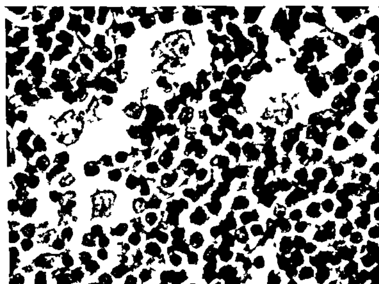


FIG 7 4
Lymphocytes interspersed with isolated reticulum cells (H and E ×450)



FIG 7 1

Lymph node in reticular lymphoma showing destruction of normal architecture by a dense sheet of cells with some fibrous intersections (H and E ×25)

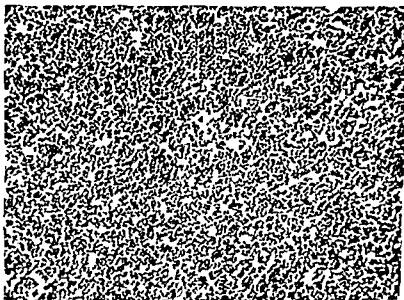


FIG 7 2

Diffuse sheet of small round cells with occasional interspersed larger cells (H and E. ×110)

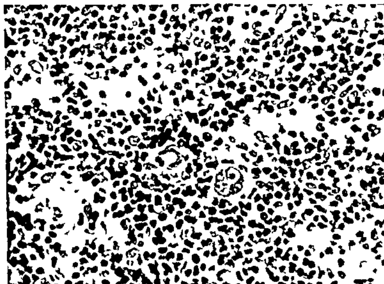


FIG 7 7

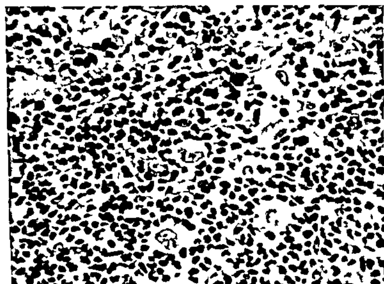


FIG 7 8

FIGS 7 7 and 7 8

Lymphocytes and scattered reticulum cells (H and E × 280)

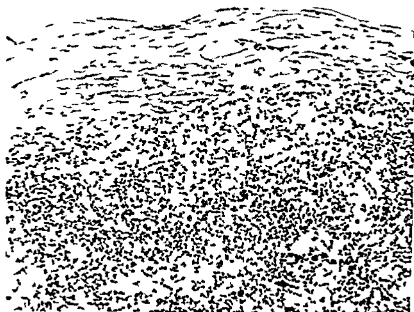


FIG 7 5
Proliferating lymphocytes and scattered reticulum cells bounded by an area of fibrosis (H and E × 110)



FIG 7 6
Lymphocytes and scattered reticulum cells (H and E × 110)

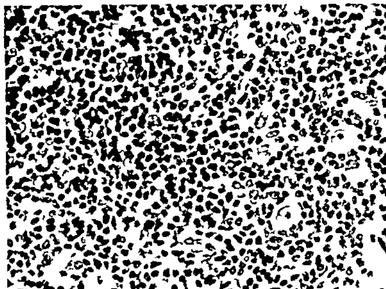


Fig 7 12

Lymphocytes and scattered isolated reticulum cells (Case No 8 first biopsy) (H and E × 80)

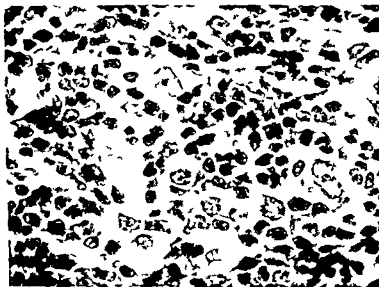
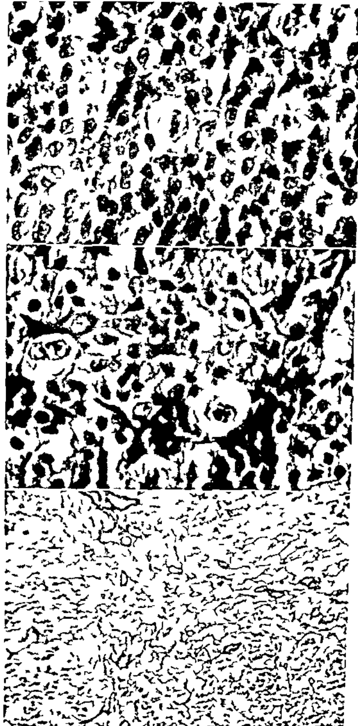


Fig 7 13

Lymphocytes and scattered isolated reticulum cells (Case No 8 first biopsy) (H and E ×450)



FIGS 7 9, 7 10 and 7 11

FIGS 7 9 and 7 10

Various views of interspersed lymphocytes and reticulum cells (H and E, ×405)

FIG 7 11

Reticulin impregnation (×100)

CHAPTER 8

HODGKIN'S DISEASE

(*Synonyms* Hodgkin s granuloma Lymphadenoma
Lymphogranuloma malignum
Fibromyeloid medullary reticulosis
and many others)

HODGKIN S disease is retained as the title for this condition as it is the most widely understood term It has been in use throughout the world for nearly one hundred years since the time of its introduction by Wilks (1856) and until a great deal more is known about tumour aetiology in general there seems little point in changing it It is the heading used by the Quarterly Cumulative Index

It is a tumour of lymphoid tissue where both reticulum cells and lymphocytes are found in almost equal proportions and from the point of view of malignancy it occupies a position in the mixed cell group of tumours between reticular lymphoma and the anaplastic sarcomas of lymphoid tissue A considerable wealth of references to the literature of Hodgkin s disease is included in a survey by Hoster *et al* (1948)

Incidence

Hodgkin s disease is the commonest tumour of this group 190 of the 410 cases in the series are thus classified accounting therefore for 46 1 per cent of the total (Table 1) Gall and Mallory (1942) gave 30 per cent of their cases this diagnosis

Sex and Age Incidence

All authors are in agreement that males are far more frequently affected than females in this disease and this fact is born out in the present series where the ratio of males to females was 2 6 to one (Table 3)

As regards age incidence cases are on record in all decades and examples in young children and even in the newborn are recorded (Priesel and Winkelbauer 1926 Charache 1946) The youngest proved example in our series was a male child aged three years and the oldest patient was a man aged seventy There is however a marked preponderance of cases in the third and fourth decades and 120 cases (63 1 per cent) were first diagnosed between the ages of twenty and forty years (Tables 4 5)

Wallhauser (1933) said that cases of Hodgkin s disease developing during the period of puberty were strikingly few in number and Jackson and Parker (1947) have suggested that the disease affects several members of one family more frequently than can be accounted for by chance These facts have not

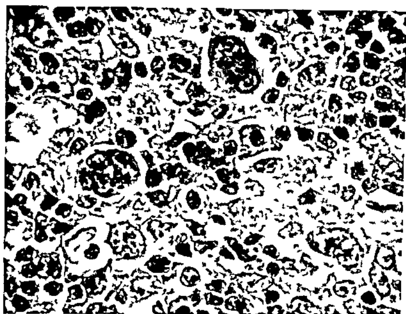


FIG 7 14

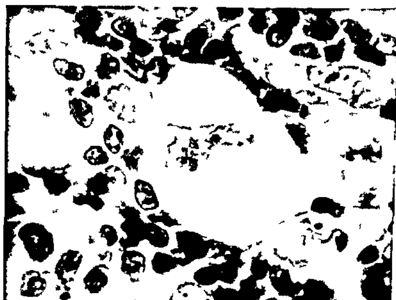


FIG 7 15

FIGS 7 14 and 7 15

Two areas from Case No 8 after more malignant course had supervened showing increased number and bizarre nature of giant reticulum cells (H and E ×450)

occasional case is seen when these nodes do not become abnormal at some stage of the disease

Occasionally isolated groups of glands may remain as the sole site of disease throughout but most commonly generalised spread occurs

Other organs most frequently affected by the disease are those containing large quantities of reticulo-endothelial tissue—spleen liver and bone marrow —and of these spleen involvement is the most common (Figs 8 2 8 3 and 8 4) 50 per cent of cases in this series were affected while 20 per cent showed bone marrow (Figs 8 5 8 6) and liver involvement (Figs 8 7 8 8) Four cases have been seen where the site of primary involvement from the clinical point of view was in the spleen (Table 12) but liver and bone marrow have only been affected later in the disease process

TABLE 12

PRESENTING SYMPTOMS AND PRIMARY SITES OF DISEASE IN HODGKIN S DISEASE

175 Cases available for Analysis

Presenting Symptoms		
1 Lump	136 =	77 6%
2 Tiredness	13 =	7 4%
3 Cough	9 =	5 1%
4 Pain	9 =	5 1%
5 Pruritis	3 =	1 8%
6 Pyrexia	2 =	1 2%
7 Others	3 =	1 8%
Primary Site of Disease		
LYMPH NODES		
Cervical	105 =	60 %
Axillary	15 =	8 6%
Mediastinal	27 =	15 4%
Inguinal	13 =	7 4%
Femoral	1 =	0 5%
Aortic	3 =	1 8%
Occipital	1 =	0 5%
Submaxillary	4 =	2 4%
Infraclavicular	1 =	0 5%
OTHER SITES		
Spleen	4 =	2 4%
Lung	1 =	0 5%

The skin is the most frequent extra reticulo-endothelial tissue to be involved and in the Westminster series 13 per cent of cases showed cutaneous

been confirmed in a study of the cases available here and the outstanding points are of a disease more frequently found in males which may appear at any age but which shows a markedly higher incidence in the third and fourth decades

Unlike lymphosarcoma age of onset seems to bear no relationship to prognosis and both long and short survival periods are recorded at all ages

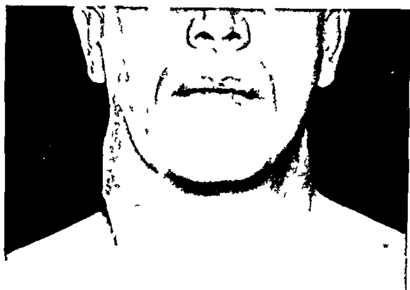


FIG 8 1
Characteristic enlargement of glands of neck in a man aged 3?

Disease Distribution

Hodgkin s disease largely affects lymphatic tissue with the lymph nodes predominating as the principal sites In assessing which group or groups of nodes are most frequently involved it is clear that during life palpation of superficial glands is easier than that of the deeper groups and for this reason alone such areas as the neck axillae and inguinal regions might be found to be affected more frequently than the mediastinum and abdomen where masses would have to progress to a greater size before being recognised Observation of areas affected at post mortem does little to shed light on this problem as in the terminal stages the disease becomes widespread in most cases

For this reason therefore the most useful approach is to assess the frequency of affection of lymph node masses as palpated during life while bearing in mind the possible fallacies which have been pointed out and paying particular attention to sites first involved

In this way it is found that the cervical lymph nodes are by far the commonest site of primary affection (Table 12) (Fig 8 1) and only a very

occasional case is seen when these nodes do not become abnormal at some stage of the disease

Occasionally isolated groups of glands may remain as the sole site of disease throughout but most commonly generalised spread occurs

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Infraclavicular	1 =	0 5%
OTHER SITES		
Spleen	4 =	2 4%
Lung	1 =	0 5%

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Fig 8 2



Fig 8 3

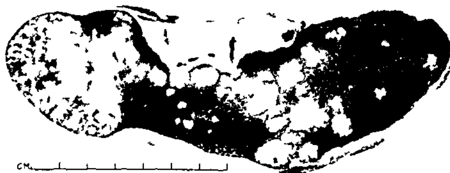


Fig 8 4

Figs 8 2 8 3 and 8 4
Varying appearance of cut surface of spleen from three different cases of characteristic Hodgkin s disease



FIG 8 5
Deposit of Hodgkin s disease in vertebrae



FIG 8 6
Hodgkin s disease infiltration in bone (H and E 60)

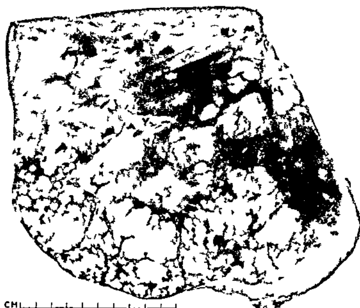


FIG 8 7
Liver diffusely infiltrated in Hodgkin s disease



FIG 8 8
Hodgkin s disease infiltration in liver (H and E ×110)



FIG 8 9
Diffuse infiltration of Hodgkin's disease in lung
(Case No 11)

manifestation at some stage thus producing one type of mycosis fungoides It is considered that this diagnosis indicates a manifestation of lymphoid tissue tumour where skin involvement brings the disease to notice and is caused most commonly by Hodgkin s disease or lymphosarcoma

Lungs and kidneys were involved in 12 per cent of the cases studied whilst only two cases have been observed with involvement of the gastro intestinal system In view of the large quantity of lymphoid material in the wall of the gastro intestinal tract it might be expected to be a common site of involvement by tumours of this tissue This is not the case Bowel involve ment in lymphosarcoma is a well recognised but somewhat unusual finding whilst in Hodgkin s disease it is very rare indeed Only two cases in the present series have shown intestinal involvement and in both cases the stomach was affected Many examples quoted in the literature are inadequately documented but occasional cases appear to be genuine Central nervous system affection in Hodgkin s disease is a well recognised clinical syndrome (Ginsburg 1927 Johnsson 1931 Winkelman and Moore 1941) producing neurological signs in the limbs or segments of the trunk accom panied frequently by severe pain In the great majority of cases where the spinal cord has become involved by the disease it seems to have resulted from epidural involvement following direct spread from neighbouring glands or other structures or by pressure from invaded or collapsed vertebrae

Occasional cases are recorded where a single organ has remained the only site of involvement in Hodgkin s disease throughout the course of the process and such an example is described in illustrative case No 11 the lung being the affected viscus (Fig 8 9)

Blood changes are neither characteristic nor diagnostic but anaemia is more constantly an associated feature of Hodgkin s disease than of the other tumours of lymphoid tissue and it tends to occur earlier in the disease Pallor particularly in the terminal stages is a striking physical sign The anaemia is usually hypochromic and red cell counts below 3 500 000 per cu mm are frequent More rarely anaemias of leuco-erythroblastic type are seen As the disease progresses blood counts suggesting aplastic anaemia are common and in the terminal stages particularly in those cases where widespread bony involvement has occurred bone marrow appearances of both aplastic and myelophthisic character are common

In rare cases of Hodgkin s disease acute haemolytic anaemia has been observed The anaemia may then be macrocytic and spherocytosis with occasionally an increased red cell fragility has been observed

Peripheral blood involvement with abnormal cells is very unusual and whilst cases are recorded in which excessively high leucocyte counts in the peripheral blood are found no example which could be termed leukaemic has been encountered in this series Eosinophilia occurred in 8 per cent of the cases but figures as high as 15 20 per cent have been recorded (Conybeare 1933 Wiseman 1936)

Natural History of the Disease

Hodgkin's disease is a progressive condition leading inevitably to death The average survival period in reported series of cases including the Westminster Hospital group is between four and five years

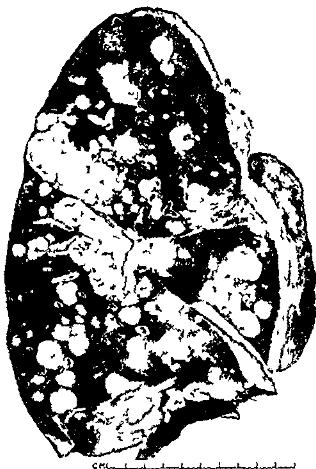


Fig 8 10
Scattered areas of Hodgkin's disease in lung in patient dying with widespread involvement of many organs

Considerable variation from case to case is common with very occasional examples of long survival of eight to ten years being found alongside others where death is rapid in eighteen months to two years As will be mentioned later in discussing the morbid anatomy of the disease there is some evidence that those cases in which marked sclerosis is found pursue a more favourable

course and it seems likely that improvement following irradiation is associated with fibrosis which closely resembles that seen in this naturally occurring sclerotic group

However no generalisation can be made and histological appearances seem to be similar in cases of varied survival The findings of Goldman (1940) Goldman and Victor (1945) and Mills and Pritchard (1935) are confirmed in that no true relation between histological appearances and prognosis can be discovered It must be stressed once again that many of the cases of so-called long survival in Hodgkin s disease may in fact belong to the group of reticular lymphoma of which full description has already been given Therefore the long surviving patients with a lymphadenopathy of this type may show when first seen the histological picture typical of reticular lymphoma with its consequent prognosis or equally well may show the appearances of fully developed Hodgkin s disease As a result of what has been said already in relation to the tumours of lymphocytic proliferation as well as the disease at present under discussion it is tempting to put the following question Is it possible that one of these diseases may progress from its more benign to more malignant form without being clinically manifest thus making the point in time at which it makes its presence obvious an important factor in producing an apparent difference between long and short survival?

There are many features already stated which seem to suggest such a phenomenon as a reasonable possibility

Despite the considerable prognostic variation in individual cases of Hodgkin s disease it is important not to lose sight of the essentially characteristic clinico pathological pattern of the disease for the long surviving cases are extremely rare In the present series only three (2 4 per cent) survived ten years (Table 13) It tends to start with minimal general clinical signs of tiredness and mild anaemia together with palpable lymph nodes usually in the neck The glands are small discrete and rubbery as opposed to the much larger masses in lymphosarcoma

Progress is inexorably towards death but remissions frequently completely unexplained are very common Generalisation of the disease almost invariably occurs into sites already noted but abnormal cells in the peripheral blood stream are very uncommon Fever during the course of the disease is well known and the characteristic remittent pyrexia of Pel Ebstein type is common As already stated examples of disease remaining localised in isolated sites are met with occasionally

A study of the Westminster Hospital series shows no evidence that either age incidence or site of affection has any relationship to prognosis in Hodgkin s disease This is a point of differentiation from lymphosarcoma

In a small but quite definite number of cases it is possible to note a change in the rapidity of advance of the disease tending to an increased malignancy and at the same time a change towards anaplasia in microscopical appearance

TABLE 13

5 YEAR SURVIVAL IN HODGKIN S DISEASE

123 Cases available for 5 Year Analysis

(i e seen before 31st December 1947)

Cases Less than 1 Year	*Cases 1 2 Years*	*Cases –3 Years*	*Cases 3 Years*	*Cases 4 5 Years*	*Cases More than 5 Years*
6	2[illegible]		12	18	1 (d ad) 31 (alive) — 43

Of those which died (12 cases) after 5 years

Cases 5 6 Years	*Cases 6 7 Years*	*Cases 7–8 Years*	*Cases 8 9 Years*	*Cases 9 10 Years*	*Cases More than 10 Years*
3	4	1	2	1	1

Of those remaining alive at a period more than 5 years (31 cases)

Cases 5 6 Years	*Cases 6 Years*	*Cases 7 8 Years*	*Cases 8 9 Years*	*Cases 9 10 Years*	*Cases More than 10 Years*
9	6	8	5	1	2

= 34 96% 5 year survival
= 2 4% 10 year survival

of affected tissue can be demonstrated (Cases 12 and 13) (Figs 8 33 37 and 10 15 20)

This type of histological change not necessarily associated with any alteration of clinical picture has been considered very common by a number of authors It is in keeping with the general principle of progressive anaplastic change already expressed in relation to all tumours of lymphoid tissue Custer and Bernhard (1948) have quoted 39 per cent of 138 cases autopsied as showing a complete alteration of histological pattern between the original biopsy and subsequent post mortem material Jackson and Parker (1947) and Herbut *et al* (1945) have also drawn attention to this change

In the present series forty five cases have been studied at autopsy and in the majority of these a picture of increased anaplasia was seen as compared with the original biopsy In view of their large series of cases in respect to this particular point it seems reasonable to accept the figure of Custer and Bernhard

The manner of spread and metastases in Hodgkin s disease presents the same problem as has been discussed already in relation to lymphosarcoma and for the same reasons it is felt that multifocal origin and metastasis together account for generalisation in this disease

The survival rates at Westminster Hospital (Tables 13 and 14) show 34 96 per cent of cases alive after five years with an occasional case living for eight to ten years 39 08 per cent of cases were dead under three years and

TABLE 14

3 YEAR SURVIVAL IN

HODGKIN'S DISEASE

151 Cases available for 3 Year Analysis

(Cases seen before 31st December 1949)

Cases Less than 1 Year	*Cases 1 2 Years*	*Cases 3 Years*	*Cases More than 3 Years*
7	26	26	92

= 60 92% 3 year survival

no relationship with age sex site of disease or histological picture has been discovered to account for this difference The only feature which in a general way is taken to indicate the stage of advancement is an assessment of the spread of the disease on the principle that the more widespread the disease the more advanced it has become and the shorter is its expected survival (Allchin 1952)

Aetiology

The probability that some inflammatory organism is the cause of Hodgkin s disease has been investigated by numerous workers and ever since the early researches of Sternberg the tubercle bacillus has been incriminated on many occasions Thus Lichtenstein (1921) Frankel and Much (1923) and L Esperance (1929) are among those who have believed that some form of tubercle bacillus is responsible for causing the disease whilst Van Rooyen (1933) Branch (1931) and Jackson and Parker (1947) are some of the investigators who have been unable to confirm such beliefs The literature on the association of tuberculosis with Hodgkin s disease is considerable and

good reviews of this aspect of aetiology are to be found in the papers of Wallhauser (1933) and Sternberg (1936)

An assessment of the available material seems to suggest that there is no evidence for regarding the tubercle bacillus as a primary aetiological factor in this condition It was obvious to many early workers such as Reed (1902) and Longcope (1903) that tuberculosis was a frequent complicating factor and this is still true to-day (Fig 8 11) It is probable however that tuberculosis gains a hold because of the wasted and debilitated condition of the patients so that these cases are now less frequent as a result of the control of disease by modern therapeutic methods and in particular by the use of irradiation



FIG 8 11
Tuberculosis associated with Hodgkin s disease (H and E × 110)

An example of a case complicated by tuberculosis is given in illustrative case No 14 Many other possible inflammatory factors have been suggested as the aetiological background of Hodgkin s disease but none of the evidence so far presented has stood the test of further investigation

Various diphtheroid bacilli—one named Bacterium hodgkinii by Bunting and Yates (1913)—have been grown from tumour material Gordon (1932 1933) found that macerated material from tissues affected by Hodgkin s disease produced a paralysis usually leading to death when injected into the brain of rabbits This he thought was due to a virus action and considered it sufficiently specific to the disease to constitute a diagnostic test Later such workers as Turner *et al* (1938) Edward (1938a and b) King (1938)

and McNaught (1938) have shown that this effect seems to be due to the presence of eosinophils in the material used for injection

More recently Parsons and Poston (1939) Wise (1940) and Wise and Poston (1940) have claimed to be able to isolate organisms of the Brucella group from lymph nodes affected by Hodgkin s disease but so far no other worker has been able to confirm these findings



Fig 8 12
Hodgkin s disease infiltration in muscle (H and E × 110)

Is Hodgkin's Disease a True Tumour?

Despite the fact that no conclusive evidence exists for regarding Hodgkin s disease as an inflammatory process there still remain many authorities who feel that the case for regarding Hodgkin s disease as a malignant neoplasm is not fully proved Anderson (1948) states it is difficult to conceive a neoplasm in which the tumour cells are of so many different types This pleomorphism appears quite reasonable however if one accepts cellular origin in these cases from multipotential primitive mesenchymal cells

Examples of invasiveness in Hodgkin s disease are well known (Fig 8 12) but perhaps more acceptable evidence of the neoplastic nature of the disease is to be found in its close association with that form of anaplastic sarcoma of lymphoid tissue sometimes known as Hodgkin s sarcoma

Most pathologists agree that the appearances of this condition are those of an anaplastic form of Hodgkin s disease and that its rapidly fatal course is typical of a malignant tumour process It is also well recognised that many cases of clear-cut Hodgkin s disease merge or develop into it and as has

been stated already examples are recorded of reticular lymphoma following a similar course

For these reasons therefore it seems justifiable to regard reticular lymphoma Hodgkin s disease and the form of anaplastic sarcoma of lymphoid tissue sometimes known as Hodgkin s sarcoma as representing varying degrees of anaplasia within a single malignant disease process

For the same reasons that have been found convenient in other sites of origin to give more benign tumours different names from the more malignant ones so it is felt that subdivision based on histological appearance and clinical course is justifiable in this case providing it is made clear that a particular diagnosis at any single period of time may represent only a state of transition between the best and poorest degrees of differentiation

This same concept applies equally to the other main groups among the tumours of lymphoid tissue

Pathology

There is a considerable literature already in existence describing the morbid anatomical and histological features of Hodgkin s disease and good accounts have been given by Sternberg (1898) Andrewes (1902) Reed (1902) Longcope (1903) and Pullinger (1932) There is little to add to what they have already said on the subject of cellular appearances although some of the conclusions which they based on the histology are not now considered correct It is felt that the modern concept of Hodgkin s disease as a true tumour (Warthin 1931 Gall and Mallory 1942 Herbut *et al* 1945 Willis 1948) is the correct view

It is considered that the condition arises as the result of the differentiation of primitive mesenchymal cells to produce a variety of types including those of the reticulum and lymphocyte series together with cells producing fibrosis

In the majority of cases studied a relatively constant histological pattern is found but a tendency to anaplastic change may become apparent as the disease progresses (Case 12) (Figs 8 33 37)

The tissues affected by Hodgkin s disease present a greyish pink colour and are of rubbery consistency becoming firmer as fibrosis increases Lymph nodes are usually discrete (Fig 8 13) The spleen is frequently affected and macroscopically shows diffuse enlargement with yellowish patches of infiltra tion seen on cut surface (Figs 8 2-4)

The histological picture shows a proliferation of mixed cell type gradually replacing normal lymph node outline and producing fibrous tissue The appearances in the lymph nodes only will be described for these are identical with those found elsewhere in the body

The classical histological appearances of Hodgkin s disease may be listed as follows (Figs 8 14 26)

(1) Destruction of normal architecture
(2) Proliferation of reticulum cells and giant cells
(3) Fibrosis

and McNaught (1938) have shown that this effect seems to be due to the *presence of eosinophils in the material used for injection*

More recently Parsons and Poston (1939) Wise (1940) and Wise and Poston (1940) have claimed to be able to isolate organisms of the Brucella group from lymph nodes affected by Hodgkin s disease but so far no other worker has been able to confirm these findings

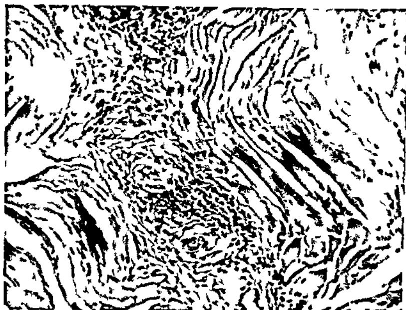


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noted however in relation to lymphosarcoma that this is a problem common to all malignant diseases and is a matter for arbitrary resolution by the individual observer It underlines the point made so clearly by Willis when he states that it is not so important to ask whether a tumour is benign or malignant but to enquire in any particular instance How benign? or How malignant?

A case of Hodgkin s disease with a typical course is described in illustrative case No 10

(4) A common but not constant finding of granulocytes in particular eosinophils and plasma cells

The proliferating reticulum cells show the particular features already described They are large cells with a single well defined nucleus in which the chromatin network is clearly seen and usually contains a well marked nucleolus which characteristically takes up a little pink dye in routine sections stained by haematoxylin and eosin (Figs 8 18 and 20)

The cytoplasm has a very faint staining capacity and this feature taken *in conjunction with the fact that* vacuolation *frequently takes place* may give the appearance of a cell lying in a gap or hole between the smaller round cells (Fig 8 21) Syncytial strands are usually seen joining adjacent cells (Figs 8 18 8 23 and 8 26)

The giant cells in this condition contain from two to five nuclei and are of *the same general appearance as the reticulum cells The cytoplasm may* be pale or may take up the eosinophil dyes quite markedly A characteristic pattern is seen when two nuclei are found in the mirror image position (Figs 8 23 8 24) It would seem reasonable to assume that these cells are a malignant variation of reticulum cells and provide the characteristic proliferating cell of the disease The significance of eosinophil proliferation raises argument Some authors feel that the presence of these cells together with others of the granulocyte series indicates a myeloid differentiation of the proliferating cells The evidence for this view is very inadequate however and in view of their inconstant appearance it is considered more reasonable to regard them as a secondary invading cell in the same way that eosinophils are frequently seen in carcinomatous lesions

The fibrosis in Hodgkin s disease is a specific feature The earliest change is an increase of the argyrophil network and subsequently collagen is laid down upon it (Figs 8 22 8 27 31) It might be expected that the more slowly growing and better-differentiated examples of this condition would show excessive fibrosis whilst the more rapidly advancing and malignant varieties would be more cellular and anaplastic Although not very conclusive there is some evidence from the material studied at Westminster Hospital that this view is correct Occasional examples of amyloid infiltration of tissues *affected by Hodgkin s disease have been recorded* and in one case in the present series amyloid degeneration was found in many of the lymph nodes examined (Fig 8 32)

Differential Diagnosis on Histological Grounds

The differential diagnosis in Hodgkin s disease presents no difficulty in the vast majority of cases as the appearances as described are quite typical In the individual case it may not be easy to decide whether a degree of anaplasia exists sufficient to warrant a diagnosis of anaplastic sarcoma of lymphoid tissue or in other cases the borderline between reticular lymphoma and true Hodgkin s disease may be difficult to assess It has already been



Fig 8 15
Lymph node showing patchy replacement of normal architecture with an irregular cellular proliferation (H and E ×25)



Fig 8 16
Irregular replacement of normal architecture (H and E ×25)

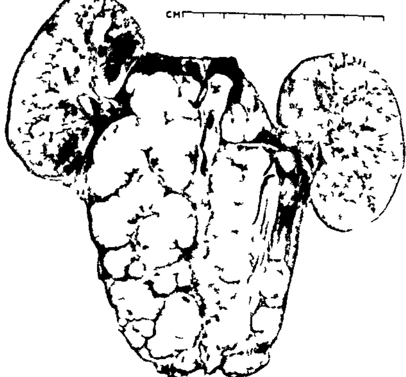


FIG 8 13
Mass of rubbery discrete lymph nodes of para aortic group removed at post mortem

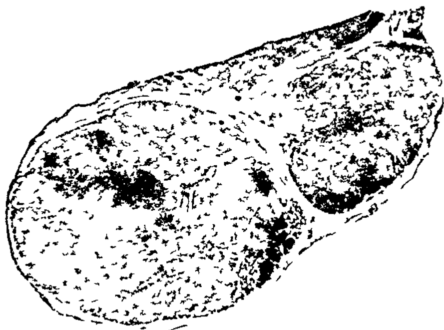


FIG 8 14
Lymph node showing replacement of normal architecture by irregular cellular proliferation with fibrous intersections (H and E ×25)

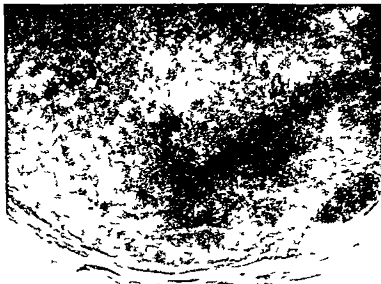


FIG 8 19
Irregular replacement of normal architecture (H and E × 25)

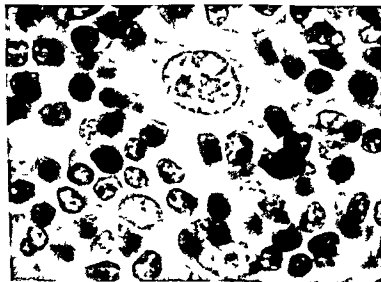


FIG 8 20
Pleomorphic cellularity including reticulum cells (H and E × 450)

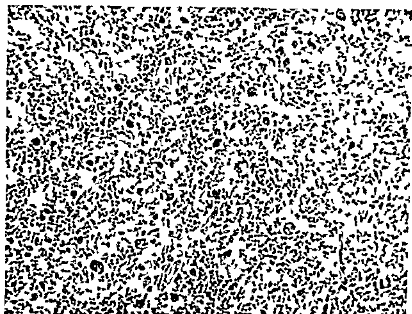


FIG 8 17
Pleomorphic cell pattern (H and E ×110)

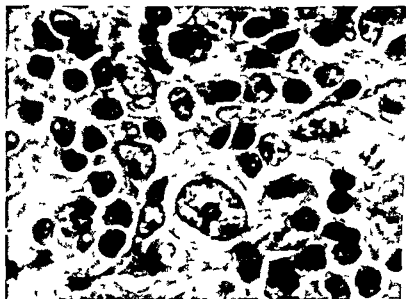


FIG 8 18
Pleomorphic cell pattern including reticulum cells (H and E ×405)

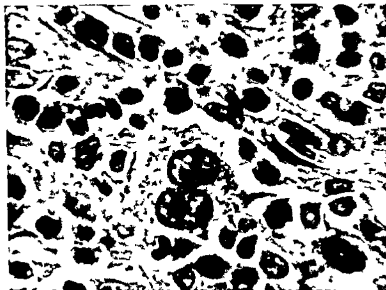


FIG 8 .3
Pleomorphic cellular proliferation showing binucleate giant cells
(H and E 405)

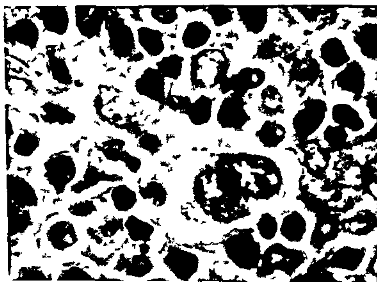


FIG 8 24
Pleomorph c cellular proliferation showing binucleate giant cells
(H and E ×450)

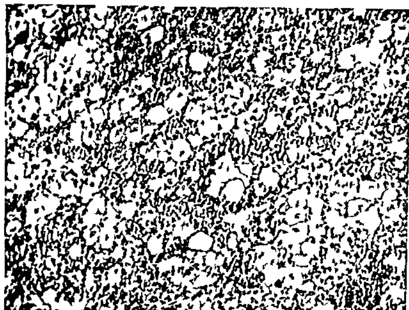


Fig 8 21
Proliferation of reticulum cells giving the appearance of cells lying in holes (H and E × 110)



Fig 8 22
Increase in reticulin pattern Reticulin impregnation (× 110)



Fig. 8.27
Lymph nodes affected by Hodgkin's disease showing marked sclerosis (H and E × 25)

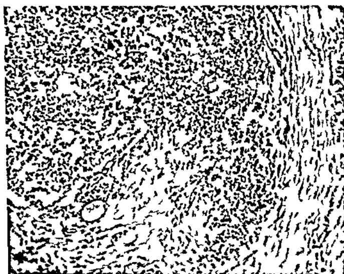


Fig. 8.28
Irregular fibrosis in Hodgkin's disease (H and E × 110)

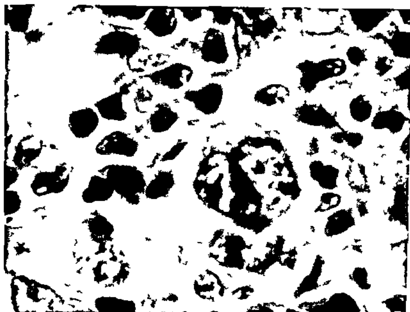


FIG 8 25

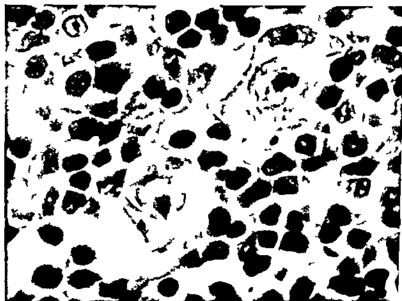


FIG 8 .6

FIGS 8 25 and 8 6
Varying types of reticulum cells (Sternberg Reed cells) from a case of Hodgkin s disease (H and E 450)

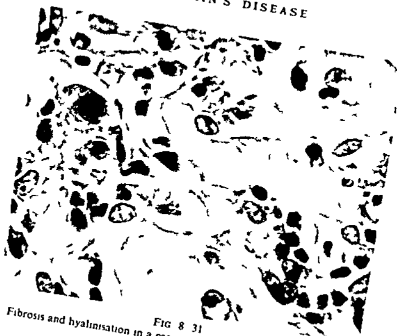


FIG 8 31
Fibrosis and hyalinisation in a case which had not received irradiation (H and E 450)

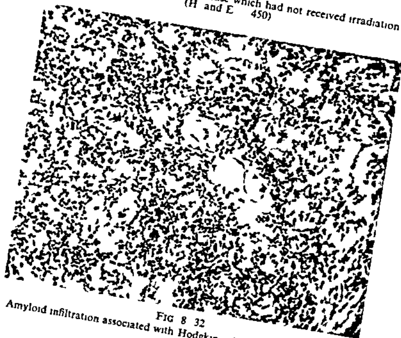


FIG 8 32
Amyloid infiltration associated with Hodgkin s disease (H and E ×110)

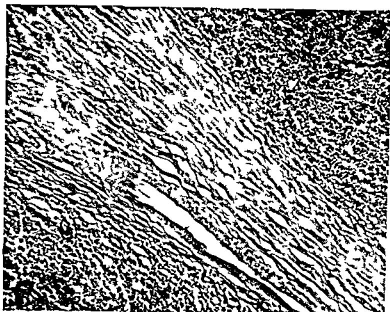


Fig 8 29
Band of dense collagen in Hodgkin's disease (H and E × 110)

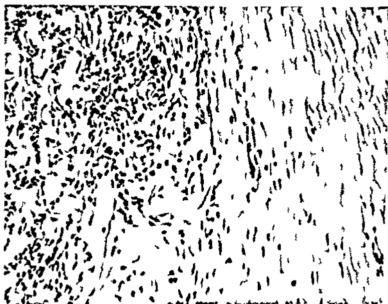


Fig 8 30
Advanced fibrosis in a lymph node taken from a patient with Hodgkin's disease who had not received irradiation (H and E × 110)

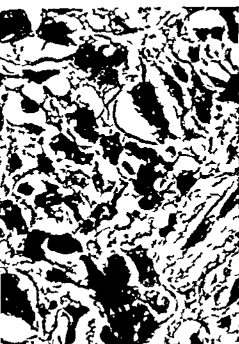


Fig. 8 35



Fig 8 36

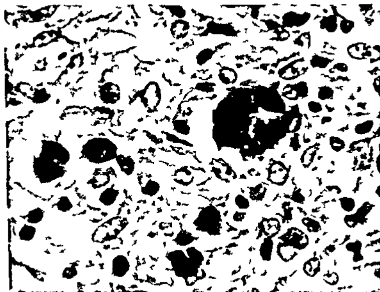


Fig 8 37

Figs 8 35 8 36 and 8 37

Three views of the same case as in Figures 8 33 and 8 34 at a later stage of the disease process when anaplastic change had occurred (H and E. ×405)

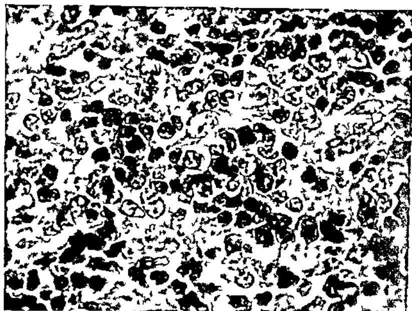


FIG 8 33

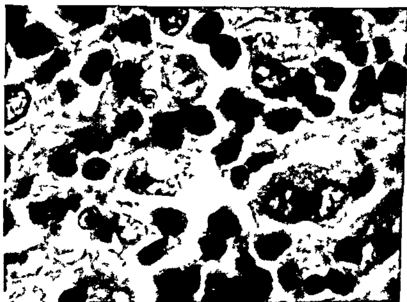


FIG 8 34

FIGS 8 33 and 8 34

Two views of a case of Hodgkin's disease as seen at first biopsy (Case No 1_) (H and E ×450)

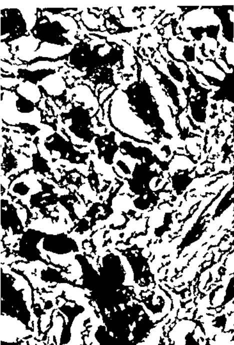


FIG 8 35



FIG 8 36

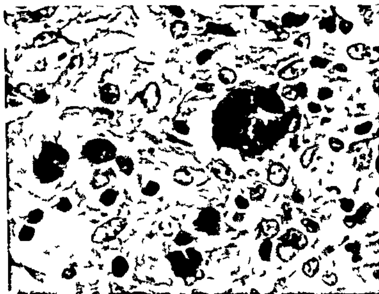


FIG 8 37

FIGS 8 35 8 36 and 8 37

Three views of the same case as in Figures 8 33 and 8 34 at a later stage of the disease process when anaplastic change had occurred (H and E ×405)

CHAPTER 9

RETICULUM CELL SARCOMA

(*Synonyms* Retothelsarcom
Lymphosarcoma reticulum cell type
Reticulocytoma)

THIS tumour was first described by Roulet in 1930 under the title of *retothelsarcom but since that time the condition has become confused* by numerous varying definitions Some authors including Ewing (1928) have believed that the reticulum cell was a primitive form of lymphocyte and that a tumour made up of these cells was simply a variety of lymphosarcoma hence the title lymphosarcoma reticulum cell type This concept is considered incorrect for the reticulum cell is believed to arise as a separate entity from primitive mesenchyme and is identical with all those cells which have been given different names such as histiocyte clasmatocyte macrophage and many others

It is therefore the primary tumours arising from this type of cell—the reticulum cell—which are to be considered here Gall and Mallory (1942) felt that this group should be subdivided into —

(1) Clasmatocytic—made up of well-differentiated phagocytic cells and
(2) Stem cell sarcoma—composed of undifferentiated pluripotential cells

It has been found impossible to interpret any differential feature between these varieties and therefore the groups described here include all those tumours made up entirely of reticulum cells—the cytologi al characteristics of which have been described earlier (p 17)

Incidence

Reticulum cell sarcoma is a rare condition twenty-one cases have been given this diagnosis in the Westminster Hospital series This accounts for 5 6 per cent of the total number of tumours of lymphoid tissue studied This figure is lower than that given in many recorded series but it must be made *clear that the diagnosis is made here only in those cases where there* is a marked preponderance amounting in the majority of cases to a uniform proliferation of well-defined reticulum cells Many authors have used the term reticulum cell sarcoma as a group title for all anaplastic sarcomas of lymphoid tissue—the next disease to be described—and have argued that there is no justification in making any further subdivision The reasons why it has been *decided to do so here may be stated as follows* —

(1) Anaplastic sarcoma of lymphoid tissue as a title includes all the poorly differentiated tumours of the group where it is frequently impossible to assess

whether an immature cell represents an early form of lymphocyte reticulum or other cell

(2) A small but definite number of tumours exist where the histological picture shows sheets of reticulum cells with very little variation from one to another Sometimes these tumours show a tendency to produce fibrous tissue and in some cases tumours of this type present as a primary lesion in bone an occurrence which has not been observed in any of the other tumours of lymphoid tissue

Sex and Age Incidence

Once again a higher incidence is found in men than in women In this series the ratio was two to one (Table 3) The cases given the diagnosis of reticulum cell sarcoma show a predominance of older patients—47 8 per cent occurred after the age of fifty years and only one case has been seen in a patient under twenty years (Table 4) The most frequently affected decades were the sixth and seventh (Table 4) (Fig 3 3)

Disease Distribution

In such a small group of cases care must be taken not to be too dogmatic In the cases studied the majority have presented with enlarged glands in the neck (Table 15) Three cases have shown primary lesions in bone and three

TABLE 15

PRESENTING SYMPTOMS AND PRIMARY SITES OF DISEASE IN RETICULUM CELL SARCOMA

20 Cases available for Analysis

Presenting Symptoms	
1 Lump	16 = 80%
2 Tiredness	3 = 15%
3 Dyspnoea	1 = 5%
4 Pain	4 = 20%
5 Cough	1 = 5%
Primary Site of Disease	
LYMPH NODES	
Cervical	7 = 35%
Axillary	5 = 25%
Mediastinal	3 = 15%
Inguinal	1 = 5%
OTHER SITES	
Spleen	1 = 5%
Bone	3 = 15%

have presented with mediastinal masses Progression of the disease to widespread tissue involvement has been the rule with generalised lymph node liver spleen and bone marrow invasions No cases with skin involvement have been seen neither have any cases with abnormal cells in the peripheral blood been studied

Natural History of the Disease

Reticulum cell sarcoma is a rapidly progressive fatal disease with 12 5 per cent of five year survivals to be recorded and 80 per cent of the cases dead in less than three years (Table 16) It is not possible in this group to

TABLE 16

SURVIVAL RATES IN

RETICULUM CELL SARCOMA

5 Year Survival

8 Cases available for 5 Year Analysis

Cases Less than 1 Year	*Cases 1 2 Years*	*Cases 2 3 Years*	*Cases 3 4 Years*	*Cases 4 5 Years*	*Cases More than 5 Years*
2	3	1	1		1

= 12 5% 5 year survival

3 Year Survival

15 Cases available for 3 Year Analysis

Cases Less than 1 Year	*Cases 1 2 Years*	*Cases 3 Years*	*Cases More than 3 Years*
2	6	4	3

= 20% 3 year survival

distinguish examples of better prognosis and higher degree of differentiation as has been the case in the lymphocytic and mixed cell types It might be expected that some cases showing a tendency to fibrosis would have a better prognosis but in the small number of cases examined this has not been true Illustrative case No 15 gives an account of typical progress in this condition

No characteristic haematological picture is seen in this disease Towards the end of its rapid course a progressive hypochromic anaemia is common

Primary Reticulum Cell Sarcoma of Bone

Three cases have been studied where lesions which have presented in bone have shown at biopsy a picture of replacement of normal architecture by a proliferation of reticulum cells These cases have subsequently developed a widespread lymphadenopathy and have died with a picture identical with the other cases of reticulum cell sarcoma in the terminal stages (Case No 16) It is clear that certain difficulties exist in distinguishing a reticulum cell prolifera tion in bone from other round cell tumours such as carcinomatous metastases particularly from the bronchus myelomatosis metastases from neuroblastoma and Ewing s sarcoma That distinction exists between reticulum cell sarcoma carcinoma neuroblastoma and myelomatosis is certain and whilst autopsy findings will serve for final proof cytological differences between the conditions must suffice for biopsy diagnosis

The characteristic plasma cell of myelomatosis serves to differentiate this disease the reticulum cell appearances already described can be distinguished from the small dark cells of a bronchogenic carcinoma or neuroblastoma whilst the demonstration of rosettes in some cases of the latter condition may be of assistance (Fig 11 18) It is however the positive finding of character istic reticulum cells which is the most important feature in making a diagnosis

The position of Ewing s sarcoma is more difficult to assess Willis (1940) has pointed out that many cases of unidentified neuroblastomas and carcino matous metastases have masqueraded as Ewing s sarcoma and some authors have suggested that Ewing s sarcoma is in fact reticulum cell sarcoma (Oberling 1928 Oberling and Raileanu 1932) Many authors however consider that Ewing s sarcoma does represent a real entity (McCormack *et al* 1952a b) Parker and Jackson (1939) feel that it can be separated on histo logical grounds from reticulum cell sarcoma and McCormack *et al* (1952a) whilst agreeing with this point of view make the suggestion that reticulum cell sarcoma of bone may represent a well-differentiated form of Ewing s sarcoma and go on to say that the larger celled types of Ewing s sarcoma merge imperceptibly into the diffuse varieties of reticulum cell sarcoma It would appear therefore that a small group of bone tumours exist where no other primary lesion can be discovered at post mortem and where the histology of the bony lesion shows small darkly staining round cells proliferating in a very scanty stroma This group fits the original description of Ewing (1939)

Pathology

Organs affected by reticulum cell sarcoma show no macroscopic features which can be used to distinguish them from other primary tumours of lymphoid tissue Tumour material is whitish in colour and the majority is rubbery in consistency Areas of fibrosis may occur as may zones of softening due to necrosis

The histological picture consists of a replacement of normal architecture by sheets of large cells varying from 12 20μ in diameter with large well defined nuclei frequently containing one or more somewhat eosinophilic

nucleoli (Figs 9 1 5) The cytoplasm is irregular in quantity and outline and stains palely with eosin Silver impregnated sections show reticulin fibres scattered diffusely among the cells and sometimes interlacing prolongations join one cell with its neighbour Giant multinucleate forms may occur but are not very common Mitoses are seen but are not very frequent Areas of necrosis and fibrosis are seen scattered irregularly through the cellular mass and fibrosis may be of considerable degree

Differential Diagnosis on Histological Grounds

It is seen that the cell type in this condition is identical with one of those found in Hodgkin s disease and it is at once clear that in a case where fibrosis occurs differentiation from Hodgkin s disease might be difficult There is however no polymorphism and it has been the practice to confine the diagnosis of reticulum cell sarcoma to those cases where the histological make up shows a very marked predominance of typical reticulum cells (Figs 9 1 5)

An important differential problem is to distinguish reticulum cell sarcoma from a carcinomatous metastasis in a lymph node where cells superficially resembling reticulum cells frequently occur In this connection the following features are of importance

(1) A carcinoma metastasising in a lymph node is a sinus proliferation pushing aside normal lymphatic tissue The reticulum cell sarcoma is primary in the lymphatic tissue and destroys it as it proliferates (Figs 10 5 6 and 11 11 12)

(2) The carcinoma however anaplastic may show some tendency to acinar or alveolar pattern The reticulum cell sarcoma produces sheets of cells without pattern

(3) The reticulin distribution as seen following silver impregnation methods shows groups of cells surrounded by reticulin in carcinoma In reticulum cell sarcoma reticulin fibrils run diffusely between individual cells



FIG 9 1
Replacement of normal lymph node architecture by a diffuse proliferation of reticulum cells (H and E × 110)

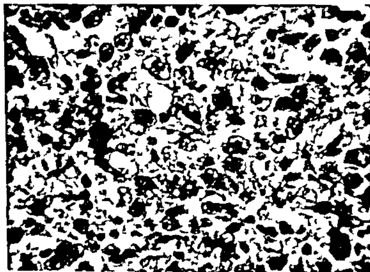
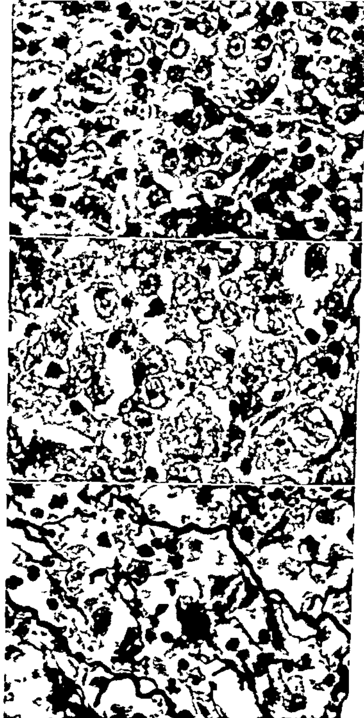


FIG 9 2
Diffuse sheets of reticulum cells (H and E × 450)



Figs 9 3 and 9 4

Diffuse sheets of reticulum cells (H and E × 405)

Fig 9 5

Reticulin impregnation showing diffuse strands of reticulin fibres some of which are arising from the periphery of cell cytoplasm (× 405)

CHAPTER 10

ANAPLASTIC SARCOMA OF LYMPHOID TISSUE

(*Synonyms* Lymphoblastic reticulosarcoma
Hodgkin s sarcoma
Stem cell sarcoma etc)

THIS group of tumours includes the anaplastic variants of all three types of differentiation It might be argued that it would be better to include with each principal differentiating type its own most anaplastic form but it has been found impossible in a study of the tumours to distinguish one type from another when anaplasia becomes extreme This is not surprising if one accepts the theory of common origin from a primitive mesenchymal stem cell The group is separated therefore not as an indication of any fundamental cytological difference but simply for convenience of diagnosis and prognostic assessment The principal types which go to make up this group will be the anaplastic variants of lymphocytic differentiation sometimes called lymphoblastic reticulosarcoma (Figs 10 2 7) and the anaplastic variants of mixed cell differentiation sometimes called Hodgkin s or polymorphic reticulosarcoma (Figs 10 8 11)

TABLE 17

PRESENTING SYMPTOMS AND PRIMARY SITES OF DISEASE IN
ANAPLASTIC SARCOMA OF LYMPHOID TISSUE
68 Cases available for Analysis

Presenting Symptoms

1	Lump	42	=	61 5%
2	Tiredness	6	=	8 9%
3	Dyspnoea	4	=	5 9%
4	Pain	6	=	8 9%
5	Cough	5	=	7 4%
6	Indigestion	2	=	2 9%
7	Anorexia	1	=	1 5%
8	Night sweats	1	=	1 5%
9	None	1	=	1 5%

Primary Site of Disease

LYMPH NODES			
Cervical	32	=	47 05%
Axillary	5	=	7 4%
Mediastinal	15	=	22 05%
Inguinal	4	=	5 9%
Aortic	3	=	4 4%
Submaxillary	2	=	2 9%
Occipital	1	=	1 5%
OTHER SITES			
Thyroid	1	=	1 5%
Tonsil	2	=	2 9%
Skin	1	=	1 5%
Widespread	2	=	2 9%

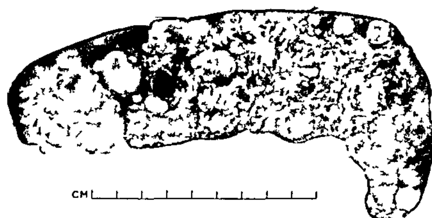


FIG 10 1
Diffuse infiltration of the spleen in a case of anaplastic sarcoma of lymphoid tissue

Incidence

Seventy cases of the Westminster Hospital series were placed in this group thus accounting for 16 9 per cent of the total number This figure cannot be compared directly with any other published series for the reasons of grouping already stated (Table 1)

Age and Sex Incidence

The male preponderance seen in the other tumours of this series is again encountered in this group The ratio was 2 25 to 1 (Table 3) The disease is

more frequent among the older age groups 40 per cent present after the age of fifty whilst only 5 7 per cent have been seen under the age of twenty years (Table 4) The most frequently affected decades were the sixth and the seventh (Table 5 Fig 3 3)

TABLE 18

SURVIVAL RATES IN
ANAPLASTIC SARCOMA OF LYMPHOID TISSUE

5 Year Survival

38 Cases available for 5 Year Analysis

Cases Less than 1 Year	*Cases 1 2 Years*	*Cases 2 3 Years*	*Cases 3 4 Years*	*Cases 4 5 Years*	*Cases More than 5 Years*
26	3	3	1	3	2

=5 26% 5 year survival

3 Year Survival

46 Cases available for 3 Year Analysis

Cases Less than 1 Year	*Cases 1 2 Years*	*Cases 2 3 Years*	*Cases More than 3 Years*
31	5	3	7

=6 25% 3 year survival

Out of 46 available 31 died in less than 1 year=67 4%

Disease Distribution

The anaplastic sarcomas of lymphoid tissue tend to be very widespread in their distribution but there is a marked tendency for cervical and mediastinal gland masses to be primarily affected Occasional examples have been seen where the disease has remained confined to one isolated group of lymph nodes and this feature will be referred to again in relation to prognosis As the disease progresses widespread involvement of most tissues in the body occurs (Fig 10 1)

Natural History of the Disease

In the vast majority of cases of this type an extremely rapid downhill course is pursued with increasing anaemia and cachexia associated with widespread involvement of tissues by the disease Lymph nodes and tumours show

considerable and speedy enlargement partly due to the rapidity of cellular proliferation and partly to haemorrhages into the substance of the masses Only 5 26 per cent of cases of this type have lived for five years and the average survival is between six and eighteen months with 67 4 per cent of the cases dying in less than one year and 93 75 per cent in less than three years (Table 18) (Case No 19)

Mention has already been made of occasional cases remaining localised in one site and one such case seems worthy of special description in view of its remarkable survival (Case No 17) Here was a case where the histological appearances of the affected lymph nodes indicated extreme anaplasia and yet the patient has remained alive and well for many years No explanation is offered for this remarkable happening except to comment that most series of cases of tumours of lymphoid tissue contain isolated examples of extreme anaplasia where good results have followed removal of affected glands at a time when the disease is apparently confined to a single area For reasons already discussed it is seldom possible to be certain whether a lymph node enlargement is in fact solitary even if it appears to be so however in those cases where it seems probable that only one area is involved at the time when the patient is seen it may be justifiable to consider radical surgery in view of the occasional good results which may ensue

Pathology

Soft whitish non-encapsulated masses showing a marked tendency to necrosis and haemorrhagic degeneration are the feature of this group of disease Ulceration of the skin by underlying lesions is an unusual feature of the tumours of lymphoid tissue and in the few cases where it has been seen in the series at Westminster Hospital the histological picture has been of ana plastic type A case illustrating this point is described in illustrative case No 13 It seems likely that in many of the cases where ulceration takes place it may be partly the result of breakdown in a previous biopsy wound or the irradiation in such a site (Figs 10 12 14) Case No 13 is also an example of progressing malignancy from Hodgkin s disease into a more anaplastic form and is worthy of study from this point of view also (Figs 10 12 20)

The histological picture in anaplastic sarcoma of lymphoid tissue is one of pleomorphic cell proliferation showing anaplasia and rapid growth as demon strated by numerous normal and abnormal mitotic figures Great variability of histological appearance is seen Not only may the pattern and cytology differ from one mass to another in the same patient but widely dissimilar pictures may be observed in different parts of the same tumour (Figs 10 7 8)

The principal cells involved in the proliferation are immature forms of lymphocyte and reticulum cell but as these lymphoblasts and stem cells as they may be called are in their turn developed from a common parent cell—the primitive mesenchymal cell—it is not surprising that their cytological characteristics are very similar *making differentiation an impossibility in*

many cases The cells are large with irregular cytoplasm and their nuclei contain irregularly clumped chromatin frequently seen undergoing mitosis

Many authors have described different varieties of these anaplastic tumours under such titles as lymphoblastic reticulosarcoma syncytial reticulum cell sarcoma and Hodgkin s sarcoma thus indicating a proliferation of the pre cursors of lymphocytes reticulum cells or a mixture of cells respectively Whilst in some tumours and certainly in some areas of tumours such cyto logical specificity can be made out on occasion (Figs 10 4 10 11) it has been found that differentiation of the primitive cells is so uncertain as to be worth less Further strength is added to this argument by pointing out that there is no evidence of any prognostic difference between any of the tumours included in this group

Differential Diagnosis Based on Histological Appearances

The principal diagnostic problem lies with anaplastic carcinomatous deposits in lymph nodes but rarely even in the most rapidly advancing tumours is there seen such a degree of cellular variability with giant cell forms and mitoses as in the anaplastic sarcomas of lymphoid tissue Again the feature already mentioned may prove of assistance namely that a metastasis is a proliferation in sinuses pushing aside and infiltrating normal structures whereas the primary tumour is arising from the lymphoid tissue and therefore destroying its architecture as it grows (Figs 10 6 7 and 11 11 12)

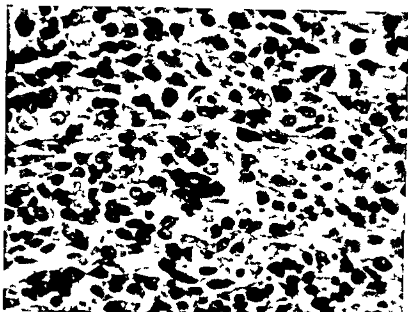


FIG 10 2

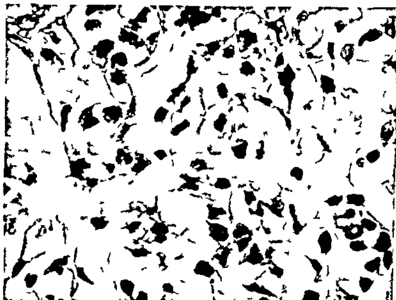


FIG 10 3

FIGS 10 2 and 10 3

Anaplastic cellular proliferation taken from areas showing an appear ance predominately lymphoblastic in type This type of picture is one sometimes named lymphoblastic reticulosarcoma (H and E × 450)

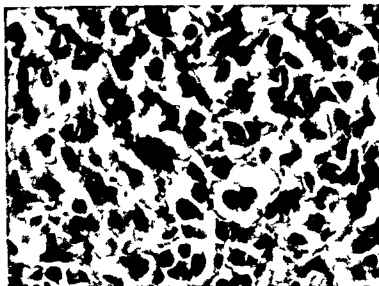


FIG 10 4
Anaplastic cellular proliferation taken from areas showing an appearance predominately lymphoblastic in type This type of picture is one sometimes named lymphoblastic reticulosarcoma (H and E ×405)

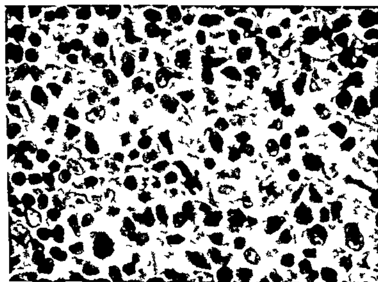


FIG 10 5
A further example of an apparently lymphoblastic area Note the mitotic figure (H and E ×450)

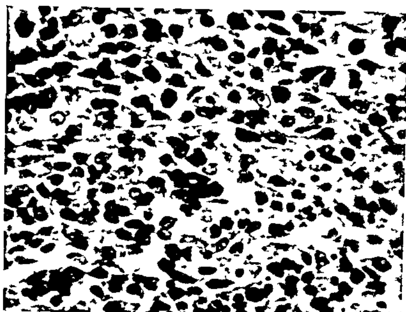


FIG 10 2

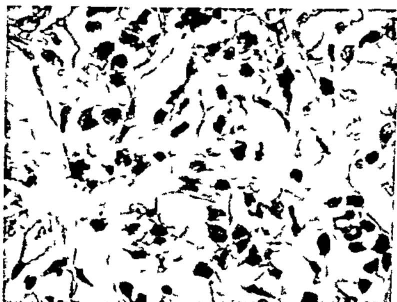
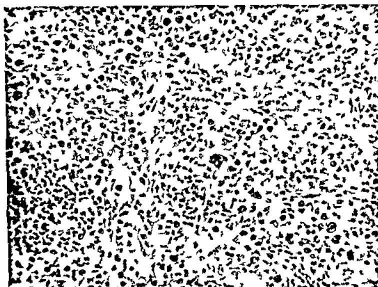


FIG 10 3

FIGS 10 2 and 10 3

Anaplastic cellular proliferation taken from areas showing an appearance predominately lymphoblastic in type This type of picture is one sometimes named lymphoblastic reticulosarcoma (H and E. ×450)



FIGS 10 8
Replacement of normal architecture of lymph node by an anaplastic pleomorphic cellular patternwork (H and E × 110)



FIG 10 9
Area of necrosis in a pleomorphic cellular proliferation (H and E × 110)

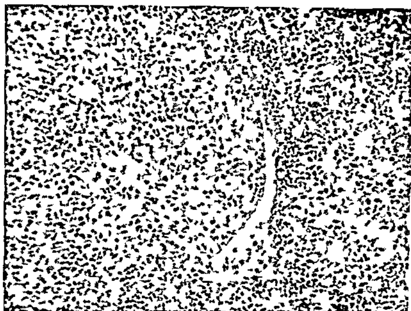


FIG 10 6
An anaplastic sarcoma proliferating up to but not invading a lymphatic sinus Where this can be seen it provides a useful differential feature from a metastasis where proliferation is arising in the sinus primarily Compare Figures 11 11 and 11 12 (H and E × 110)

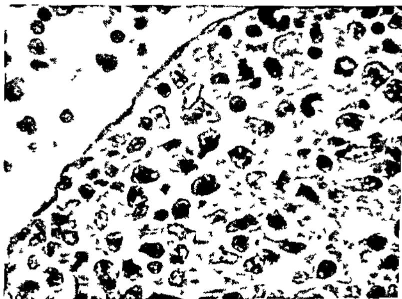


FIG 10 7
A higher magnification of the sinus area of Figure 10 5 (H and E × 450)



Fig 10 12



Fig 10 13



Fig 10 14

Figs 10 12 10 13 and 10 14

Three photographs showing a progressive ulcerative lesion associated with a lymph node mass in the right supraclavicular fossa (Case No 13)

Figure 10 12 Taken before irradiation therapy had commenced
Figure 10 13 After treatment when there is considerable ulceration
Figure 10 14 Post mortem appearance showing extensive tissue destruction

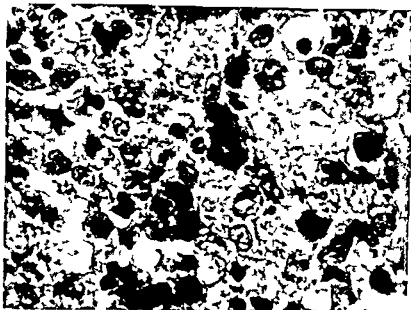


Fig 10 10

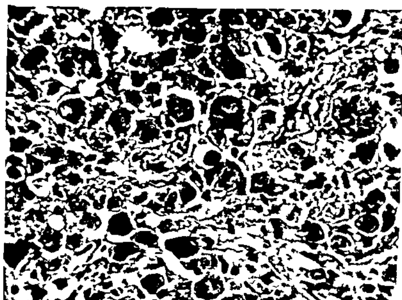
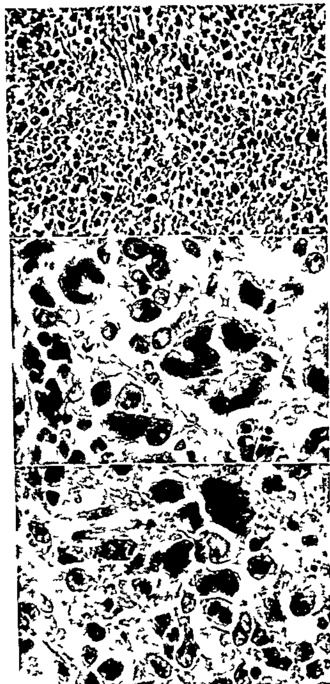


Fig 10 11

Figs 10 10 and 10 11

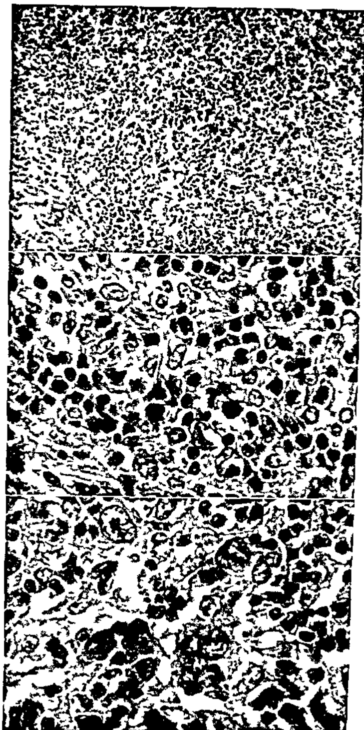
Anaplastic cellular areas showing numerous giant cells This picture is sometimes named Hodgkin s sarcoma " (H and E × 450)



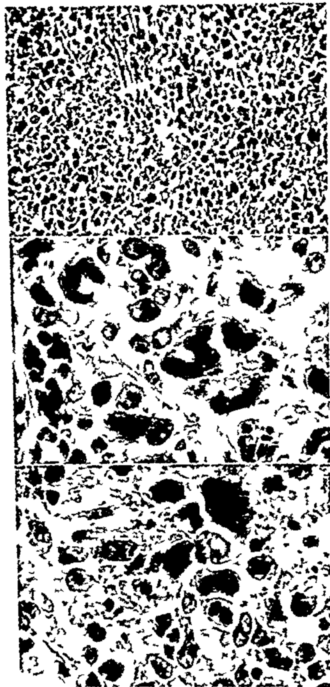
FIGS 10 18 10 19 and 10 20

Hodgkin s disease (Case No 13) after it had become more anaplastic

Figure 10 18 (H and E × 110)
Figure 10 19 (H and E × 450)
Figure 10 0 (H and E × 450)



FIGS 10 15 10 16 and 10 17
Hodgkin s disease (Case No 13) at the time of the first biopsy
Figure 10 15 (H and E ×110)
Figure 10 16 (H and E ×450)
Figure 10 17 (H and E ×450)



Figs 10 18 10 19 and 10 0

Hodgkin s disease (Case No 13) after it had become more anaplastic

Figure 10 18 (H and E × 110)
Figure 10 19 (H and E × 450)
Figure 10 0 (H and E × 450)

CHAPTER 11

PROBLEMS OF DIAGNOSIS

HAVING defined and discussed the varieties of primary tumours of lymphoid tissue met with it is now important to turn to some general account of differential diagnosis for so far only passing references to certain aspects of this topic have been made

It seems wise to begin such a discussion by describing the problem as it presents for diagnosis and giving a brief survey of the diagnostic methods available and their relative usefulness

A patient is seen with an enlargement of a group of lymph nodes appearing as a lump Goldman (*1940*) quotes *79* per cent of his patients suffering from tumours of lymphoid tissue as presenting in this way and Allchin (1952) gives a figure of 73 per cent for Hodgkin s disease and 77 per cent for lymphosarcoma Other less common presenting signs are malaise cough and pruritus In the vast majority of cases therefore it is by means of a lymph node biopsy that a diagnosis is made and a careful account of biopsy tech nique and tissue examination is justifiable

In performing the biopsy which is nearly always of a lymph node the following points should be borne in mind

(1) SELECTION OF NODE Very often selection is impossible as there is *only one enlargement present When choice can be made however inguinal* and cervical glands should be avoided as both these sites are commonly affected by non specific inflammatory changes which may produce conflict ing histological appearances The lymph node selected should be removed in its entirety taking great care not to damage the capsule at the time of operation The importance of this lies in the fact that it is essential to study the architecture of the node and if the capsule is destroyed this may be so *upset as to render its assessment impossible* Where practicable it is an advantage to take with the gland a little of the connective tissue around it

If during the removal of the lymph node there is considerable compres sion or excessive pulling on the tissues an artefact may result in the histo logical preparations which is easily recognisable once the possibility of its occurrence has been realised The changes are most commonly seen towards the edges but may on occasion appear anywhere in the sections Groups of cells are seen which tend to produce a pattern of streaming as their cyto plasm has been disrupted and their nuclei are pulled out into long strands which usually stain more deeply with haematoxylin than their neighbours Isolated clumps of chromatin from fragmented nuclei are also seen (Figs 11 1 4)

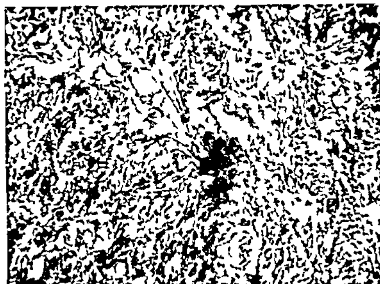


FIG 11 1



FIG 11 2

FIGS 11 1 and 11 2

Artefact of hyperchromatic spindle shaped cells which occurs following compression (H and E ×110)

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FIG 11 1



FIG 11 2

FIGS 11 1 and 11 2

Artefact of hyperchromatic spindle shaped "cells" which occurs following compression (H and E × 110)

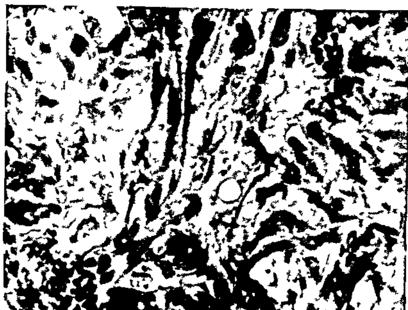


FIG 11 3



FIG 11 4

FIGS 11 3 and 11 4

Elongated spindle shaped cells produced by rupture and fragmentation of chromatin (H and E ×450)

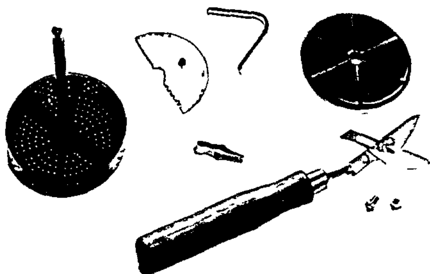


FIG 11 5
(1) Double bladed knife showing one retaining screw removed ( ) Perforated cover and clip made to fit container of automatic tissue processor

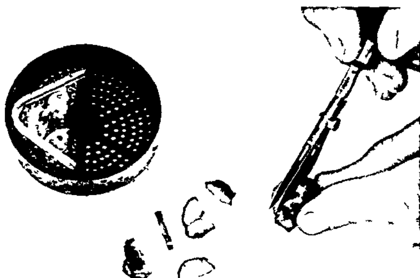


FIG 11 6
Example of method of cutting pieces showing the clip holding the flattening device in position

(2) FIXATION The biopsy material must be placed into fixative immediately At Westminster Hospital the routine solutions used for fixing lymph nodes are Formol Zenker Helly s Fluid or 4 per cent formol saline The *main point of importance in relation to fixation is the fact that the capsule* prevents penetration and it should be made a rule that if the operating theatre staff is responsible for placing the tissue in fixative each lymph node should first be bisected for in this way adequate penetration is ensured In the case of very large masses it is necessary to cut the material into slices not more than 1 cm in thickness otherwise penetration to the deeper areas does not occur It should also be stressed that a volume of fluid one hundred times that of the tissue concerned should be used When the lymph node is cut before fixation its surface bulges and care must be taken to trim this before embedding or the final sections will not demonstrate the capsule This slight inconvenience is offset by the fact that good penetration is obtained Under ideal circumstances *where the laboratory is in close contact with the* operating theatre the following routine is recommended

(*a*) Immediately following surgical removal tissues are washed in isotonic saline and placed in a refrigerator at 0 C 4 C until they can be cut up

(*b*) *Lymph nodes are bisected or in the case of large masses are sliced* at 1 cm thickness The refrigeration prevents autolysis renders the tissue just firm enough to make cutting easy and obviates initial surface bulging

A twin bladed knife with the distance between the blades set at $\frac{1}{8}$ in order to produce slices of exactly correct thickness for fixation dehydration and blocking has been found useful This technique has the obvious advantage of producing uniform results and is found to be of particular value where the modern automatic tissue processors are used (Figs 11 5 and 11 6)

(*c*) The selected areas are placed between perforated plastic sheets which can be clipped together lightly so as to prevent curving or bulging of the slice during fixation (Fig 11 7) Formol Zenker and 4 per cent formol saline are used routinely If an automatic tissue processor is in use these devices for flattening can be made to fit the containers of the individual machine (Figs 11 5 and 11 6)

It cannot be overemphasised that no amount of careful section cutting or staining can make up for an unwise selection of lymph node for biopsy or a failure to guarantee proper fixation when once removed Thus it is a regrettable fact that an unnecessarily large number of lymph node biopsies are still rendered useless or even misleading by a failure to observe these *simple* rules

Lymph nodes are composed of cells which tend to be hyperchromatic and closely packed with only a small amount of stroma It is therefore necessary to make absolutely certain that sections are cut at not more than 4 or 5μ *thickness*

Routine haematoxylin and eosin staining serves all that is necessary for diagnosis in the majority of cases but certain special staining methods are of importance

Thus mucicarmine staining and the periodic acid Schiff reaction are essential in demonstrating spores in Torulosis or for demonstrating the organisms in histoplasmosis whilst Romanowsky stains may be employed on occasion

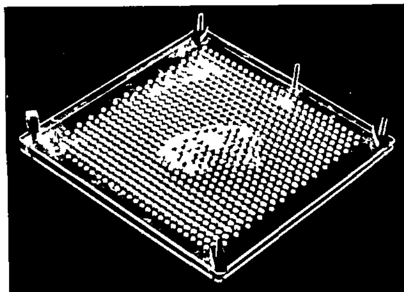


FIG 11 7
Large perforated press for maintaining flat surface of a slice during fixation

Some comments may be made here on the use of silver impregnation for the demonstration of reticulin fibres It has been the practice at Westminster Hospital routinely to stain a section to demonstrate reticulin in all cases of lymph node biopsy and the method used is that described by Gomori (1937) as modified by the author himself in a personal communication to Lillie quoted in the latter s textbook (1948) This method has proved completely satisfactory Based on the experience which has been gained in this way it would seem that this technique has two main values

(1) By outlining follicular structures where reticulin fibres are virtually absent it is frequently possible to make certain whether or not a cellular proliferation is occurring in the sinuses or in the matrix of the lymphoid tissue

(2) The majority of carcinomatous lesions show some attempt to form acinar or alveolar patterns and in these cases the cell groups will be seen to be surrounded by reticulin fibres whereas in all sarcomatous lesions including the primary tumours of lymphoid tissue the reticulin fibres run in an irregular manner between individual cells

It must be made clear however that whereas in the better-differentiated tumours characteristic reticulin patterns are to be seen the more anaplastic

(2) FIXATION The biopsy material must be placed into fixative immediately At Westminster Hospital the routine solutions used for fixing lymph nodes are Formol Zenker Helly s Fluid or 4 per cent formol saline The main point of importance in relation to fixation is the fact that the capsule prevents penetration and it should be made a rule that if the operating *theatre staff is responsible for placing the tissue in fixative* each lymph node should first be bisected for in this way adequate penetration is ensured In the case of very large masses it is necessary to cut the material into slices not more than 1 cm in thickness otherwise penetration to the deeper areas does not occur It should also be stressed that a volume of fluid one hundred times that of the tissue concerned should be used When the lymph node is cut before fixation its surface bulges and care must be taken to trim this before embedding or the final sections will not demonstrate the capsule This slight inconvenience is offset by the fact that good penetration is obtained Under ideal circumstances where the laboratory is in close contact with the operating theatre the following routine is recommended

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(*b*) Those where only rarely peripheral blood and bone marrow changes occur and where there is characteristically a lymphadenopathy with or without hepatosplenomegaly (primary tumours of lymphoid tissue)

Considerable overlap between these two groups is to be expected and has already been described Leukosarcoma or the association of a leukaemic blood picture with lymphosarcoma is the best example of this but others may be quoted such as the tumour masses (chloromas) which sometimes occur in myeloid leukaemia or the occasional examples of plasma cell leukaemia in multiple myelomatosis As an example of the merging which may occur between one cell type and another is the fact that cases of polycythaemia rubra vera have been reported which have later developed myeloid leukaemia (Parkes Weber 1921 Hall *et al* 1945) whilst Wintrobe (1946) has described an example of myeloid leukaemia which became polycythaemic for a short time followed by a period of anaemia after which the leukaemic picture returned once again

Cases where abnormal cells are proliferating in the bone marrow and appearing in the peripheral blood stream in numbers insufficient to raise the total number of leucocytes per cubic millimetre beyond a figure within the range of normality are well recognised Such cases have been called aleukaemic leukaemia and are most frequently seen among the more rapidly fatal varieties Thus Windeyer and Stewart (1952) quote a figure of twenty six cases of aleukaemic leukaemia among 359 cases of leukaemia admitted to Middlesex Hospital Of these seventeen were of acute type and eight chronic Sometimes cases may present in an aleukaemic form and later develop a typical leukaemic pattern

The varieties of leukaemia are usually subdivided according to the variety of cell which is proliferating in an abnormal manner It is the accepted custom to speak of acute and chronic leukaemias indicating the severity and prognosis of the disease It corresponds closely with the concept of anaplasia and differentiation applied to other forms of malignant disease In the acute types with poor prognosis primitive cells such as myeloblasts and lymphoblasts are found whereas in the chronic varieties better-differentiated cells such as myelocytes and lymphocytes appear

The following classification slightly modified from one suggested by Windeyer and Stewart shows these features —

(1) Acute leukaemia { Myeloblastic, Lymphoblastic, Stem-cell

(2) Chronic leukaemia { Myeloid, Lymphatic, Monocytic

(3) Aleukaemic leukaemia

the lesion the more indeterminate the reticulin outline becomes Thus whilst offering useful confirmatory evidence in many cases this staining method cannot be considered in any way a short cut to diagnosis

Other routine staining methods such as those for free iron or for melanin will be required as the occasion demands

The important factors of technique in lymph node diagnosis may be summarised as follows —

(1) Careful selection of a lymph node and the removal preferably of two or three glands complete with their surrounding connective tissue through an adequate incision

(2) Great care should be taken to ensure speedy and adequate fixation

(3) Careful cutting and staining of thin sections

In other words lymph node biopsy and examination needs perhaps a little more care at every stage of its performance than is necessary to obtain good results with other tissues When one is dealing with diseases where the results of biopsy are essential in diagnosis it is imperative that technique should be of the highest quality

It is now possible to commence a discussion of the principle conditions which must be differentiated before arriving at a diagnosis of primary tumours of lymphoid tissue

These may be considered under three main headings —

(1) Leukaemias
(2) Abnormal Depositions into Lymphoid Tissue
 (*a*) Metastatic deposits of malignant tumours
 (*b*) Lipoidoses
(3) Proliferative Reactions of Lymphoid Tissue to Inflammatory Stimuli
 (*a*) Simple reaction to non specific irritants— reactive changes
 (*b*) Proliferative reaction to certain specific inflammatory irritants— granulomatous changes

(1) Leukaemias

Virchow (1846) was the first to describe cases of a disease manifesting itself by abnormal leucocytes in the peripheral blood which were not pus cells and for this condition he suggested the title leukaemia In the years which followed as the knowledge of haematology advanced it became recognised that many cell types could be found in this disease and thus a classification of varieties was built up

It has already been made clear that no fundamental difference exists between the primary tumours of lymphoid tissue and the leukaemias Both groups of diseases are considered to be primary tumours arising from cells derived from primitive mesenchyme which may be divided for purposes of convenience into —

(*a*) Those where the disease is manifested by characteristic peripheral blood and bone marrow changes with or without hepatosplenomegaly (leukaemias)

Occasionally plasma cell tumours are found in the soft tissues around the nasopharynx and very rarely lymph node involvement of the cervical groups may occur (Hellwig 1943) In the terminal stages of multiple myelomatosis generalised involvement of organs associated with the reticulo-endothelial system such as the liver and spleen is found but in all these cases diagnosis can be made with certainty by the appearances of the plasma cells

(2) Abnormal Depositions into Lymphoid Tissue

(*a*) METASTATIC DEPOSITS OF MALIGNANT TUMOURS

The great majority of metastatic deposits in lymph nodes from malignant tumours arise from carcinomas and it is clear that the lymph node involved will usually be in a direct line of lymphatic flow from the primary tumour Complete replacement of a lymph node or blockage of a lymphatic vessel by malignant cells may lead at first to an opening up of collateral pathways and later as these become more and more devious reversal of lymph flow can occur so that deposition of cancer cells takes place in what at first sight may appear to be bizarre situations (von Recklinghausen 1885 Vierth 1895) Most metastases from carcinomas occur as a result of tumour emboli becoming separated from the main mass to be carried away in the lymphatic stream In cases of early metastasis therefore clumps of malignant cells are frequently seen in the afferent lymphatics and in the peripheral sinuses (Figs 11 8 and 11 9) For this reason malignant proliferation in a lymph node tends to progress from the most peripheral areas towards the centre Eventually the whole gland may become replaced by the tumour growth but in the majority of cases small fragments of lymphoid tissue remain even in the most advanced cases Destruction of the normal lymph node structure occurs largely as a result of compression and invasion as the malignant cells proliferate in the sinuses so that there is a clear cut line of demarcation to be seen between the new growth and the normal tissue (Figs 11 10 15)

The spread of carcinoma from one gland to another results from emboli passing from efferent lymphatics into neighbouring afferent vessels but where the malignant process has progressed to penetrate the capsule adjacent nodes may become matted together by infiltrated extracapsular tissues

As a differential diagnostic problem from primary tumours of lymphoid tissues only those cases of carcinomatous metastasis with an unknown primary are capable of giving rise to any confusion for otherwise the site of primary tumour will be apparent Cases do occur however where a lymph node or skin deposit may be the first clinical sign of disease and a biopsy of the tissue may be the first histological evidence of malignancy Willis (1934) has drawn particular attention to this phenomenon

Even in such cases as these the differentiation of carcinomatous metastasis from primary tumours of lymphoid tissue is not difficult in most instances for in glands the clear cut demarcation of the carcinoma in the sinuses from the normal tissue can be made out Usually some alveolar or acinar pattern is apparent in the carcinoma and both these features may be accentuated and

(4) Atypical leukaemias
a Eosinophilic
b Megakaryocytic
c Basophilic
d Leukosarcoma
e Plasma cell

It may be noted that this classification makes use of the term stem cell leukaemia for the acute varieties of monocytic leukaemia This conception indicates a belief that this form of leukaemia represents a proliferation of very primitive cells derived from mesenchyme When viewed histologically they have many features in common with the cells of the anaplastic sarcomas of lymphoid tissue already described The primitive nature of the cells in monocytic leukaemia has been stressed by a number of authors including Ewald (1923) Hoff (1926) Hittmair (1928) Heilmeyer (1942) Cazal (1946) and van der Meer and Zeldenrust (1948) and represents a further example of the view accepted by many authorities that all blood cells can be developed out of pluripotential mesenchymal cells (Sabin and Doan 1927 Ungar 1933 Oberling and Guerin 1934 Nordenson 1939)

Atypical leukaemias are a miscellaneous group including certain rare examples of cell types which do not fit into the other groups

Differential diagnosis between leukaemias and primary tumours of lymphoid tissue only occasionally presents any problem for in the majority of cases the diagnosis of leukaemia is made by peripheral blood or bone marrow examination

Occasionally however a case of lymphatic leukaemia or one of the acute leukaemias may present with enlarged lymph nodes This also applies quite *obviously to cases of leukosarcoma It may therefore happen that* a lymph node biopsy will be the first diagnostic procedure in such a case and it must be stated quite dogmatically that there is no histological differentiation between a case of acute leukaemia and an anaplastic sarcoma of lymphoid tissue nor is there any difference microscopically between a case of lymphatic leukaemia and lymphosarcoma

Wherever a histological diagnosis of lymphosarcoma or anaplastic sarcoma of lymphoid tissue is made it is essential to examine the peripheral blood at frequent intervals thereafter for if a leukaemic picture is not present at the time the possibility of its appearance at a later date must be considered

Further mention will be made at this point of plasma cell tumours (multiple myelomatosis) which has been briefly discussed earlier (p 21)

In the classification of leukaemias attention has been drawn to the rare appearance of plasma cells in the peripheral blood (Aschoff 1906 Patek and Castle 1936) By far the most frequent manner of presentation of this disease is in the form of bone tumours in which case biopsy or marrow puncture will enable a diagnosis to be made by the demonstration of typical plasma cells Differentiation from other round cell tumours affecting bone does not usually present any problem in view of the characteristic appearance and staining features of the cells

Occasionally plasma cell tumours are found in the soft tissues around the nasopharynx and very rarely lymph node involvement of the cervical groups may occur (Hellwig 1943) In the terminal stages of multiple myelomatosis generalised involvement of organs associated with the reticulo-endothelial system such as the liver and spleen is found but in all these cases diagnosis can be made with certainty by the appearances of the plasma cells

(2) Abnormal Depositions into Lymphoid Tissue

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FIG 11 8

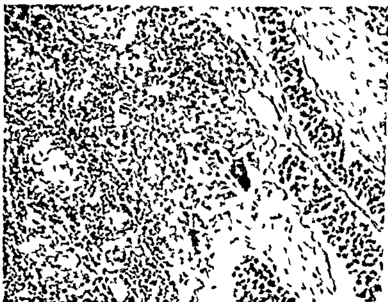


FIG 11 9

FIGS 11 8 and 11 9
Clumps of malignant cells lying in peripheral sinuses (H and E ×110)



FIG 11 10
Clumps of carcinoma cells lying in sinuses close to a well marked follicle (H and E × 110)

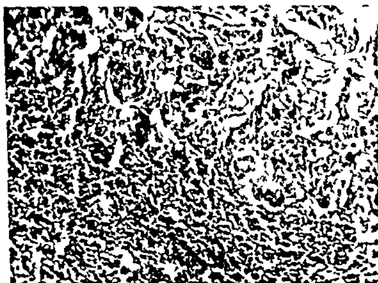


FIG 11 11
Well marked zone of demarcation between carcinoma cells in sinuses and normal lymphoid tissue (H and E × 110)



FIG 11 12
Well marked zone of demarcation between carcinoma cells in sinuses and normal lymphoid tissue (H and E × 110)



FIG 11 13
Clump of carcinoma cells showing a papilliferous pattern well d marcated from normal tissue (H and E × 110)



FIG 11 14
Small clumps of carcinoma cells lying in sinuses close to well marked follicles (H and E × 110)



FIG 11 15
Clump of carcinoma cells from a squamous cell carcinoma in a largely degenerated lymph node (H and E × 100)



FIG 11 16



FIG 11 17

FIGS 11 16 and 11 17

Metastasis from a neuroblastoma proliferating in the sinuses of a lymph node (H and E × 100)

confirmed by making use of sections impregnated with silver salts to demonstrate reticulin pattern It must be mentioned however that cases of lymph node metastasis from anaplastic carcinoma simplex (oat cell) of the bronchus may give rise to confusion in diagnosis for they produce sheets of anaplastic cells with little or no acinar arrangement

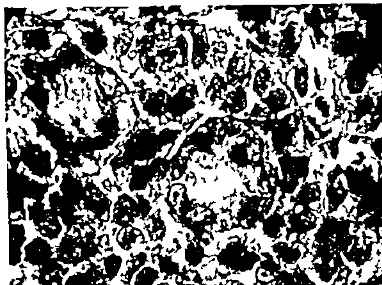


FIG 11 18
"Rosette" formation in the neuroblastoma metastasis seen in Figures 11 16 and 11 17 (H and E 405)

It is only in those rare cases where a tumour of great anaplasia has completely replaced the lymph node that real difficulty will arise and in such a case the extremely poor prognosis which can be offered makes the differentiation a matter of academic interest until an autopsy can settle the matter

Other malignant diseases which more occasionally are found as metastases in lymphoid tissue are melanomas malignant teratomas and certain embryonic tumours in childhood such as the nephroblastoma and neuroblastoma Of these the diagnosis of all but the neuroblastoma is usually quite obvious as compared with a primary tumour of lymphoid tissue in view of the quite typical characteristics of each of these tumour types In the case of the neuroblastoma the problem may present greater difficulty and such special features as rosette formation must be sought (Figs 11 16 18) In all these tumours the differential feature already mentioned in relation to carcinoma is equally applicable namely that the metastasis is a sinus infiltration invading the surrounding lymphoid tissue

Sarcomas only rarely invade lymphoid tissue (Figs 11 19 21) (Warren and Meyer 1938 Willis 1941) probably because of the paucity or absence



FIG 11 16



FIG 11 17

FIGS 11 16 and 11 17

Metastasis from a neuroblastoma proliferating in the sinuses of a lymph node (H and E × 100)

of lymphatic channels in many connective tissue areas for instance in muscle and in bone It seems likely therefore that lymphatic invasion occurs only after considerable local invasive spread has taken place and because of this the primary site of tumour origin is usually quite obvious by the time lymphoid invasion has occurred thus sarcomatous invasion of lymphoid tissue presents very little problem of differential diagnosis

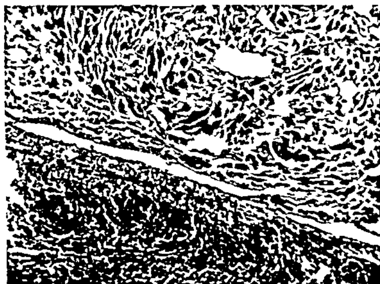


FIG 11 21
Metastasis of fibrosarcoma in an axillary lymph node (H and E × 110)

(b) LIPOID STORAGE DISEASES OR LIPOIDOSES

This group of conditions includes a variety of diseases the essential feature of which is a complex abnormality of lipoid metabolism leading to excessive storage in the cells of the reticulo-endothelial system They are therefore examples of errors of metabolism and not tumours but it is clear that the clinico-pathological picture of a multifocal disease thus produced may provide a problem in differential diagnosis from the tumours of lymphoid tissue

In accordance with the work of Thannhauser (1950) the varieties of *lipoidoses may be subdivided as follows* —

(1) Xanthomatoses

(a) Hypercholesterolaemic—Cholesterol abnormality (cholesterolosis) skin bile duct and tendon Accumulations of foamy cells with associated increased cholesterol content of blood serum

(b) Hyperlipaemic—Skin accumulations of foamy cells with associated increased fat content of blood *i e* diabetes Von Gierke s disease etc



FIG 11 19
Round cell sarcoma proliferating widely in the sinuses (H and E × 100)

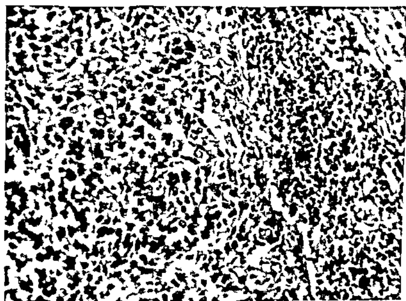


FIG 11 20
Metastasis from an osteogenic sarcoma showing the line of demarcation between the malignant mass and the lymphoid tissue (H and E × 100)

An important differential feature from the tumours of lymphoid tissue and from Hodgkin s disease in particular is the manner in which the abnormal cells proliferate in the sinuses of lymph nodes and spleen pushing aside the existing tissues which themselves retain an essentially normal pattern

Letterer Siwe disease therefore may be considered to represent the first or proliferative phase of the four pathological patterns described above where death occurs before the granulomatous or xanthomatous patterns appear

Eosinophilic granuloma of bone represents the granulomatous and xanthomatous phase of this condition where the lesions are confined to bone and in which masses of phagocytic cells and eosinophils together with numerous foam cells are seen The predominance of eosinophils and foam cells makes a histological picture unlike any of the primary tumours of lymphoid tissue which may produce bony lesions

Schuller-Christian syndrome would seem to represent the most chronic and widespread form of this lesion but once again bony distribution is the commonest feature The involvement of the base of the skull and orbital area gives rise to the polydipsia and exophthalmos which are considered characteristic of the syndrome Lymphadenopathy is relatively common but hepatosplenomegaly is rare Lung involvement in this disorder is not uncommon and the association of honeycomb lung with this group of diseases has been noted by Oswald and Parkinson (1949) The disease is chronic and tends to produce fibrosing lesions of good prognosis in its later stages The differential diagnosis of the lymphadenopathy from primary tumours does not usually provide any problem

Gaucher s disease is a generalised disorder of metabolism affecting adults and occasionally children the characteristic feature of which is the prolifera tion of large foamy cells (Gaucher s cells) (Fig 11 22) which contain the cerebroside The abnormal areas are classically confined to the lymphatic system (Fig 11 23) the liver spleen (Fig 11 24) bone marrow (Fig 11 25) and skin in contradistinction to Niemann Pick s disease which occurs diffusely throughout all organs An important feature which differentiates both Gaucher s and Niemann Pick s disease from the cholesteroloses is the formation of the foamy cells without any associated granulation tissue reaction Haemorrhage frequently occurs into the lesions with considerable associated haemosiderosis

Niemann Pick s disease is another example of a generalised metabolic disorder Characteristically it affects children with the production of cells containing sphingomyelin Any tissue in the body may be affected and a further differential feature from Gaucher s disease is the absence of any haemosiderosis at any stage of the process

The large foam cells of these lesions provide a clear-cut differential picture from the primary tumours furthermore the lymph node feature common to all lipoidoses is seen namely a sinus proliferation pushing aside tissues which tend to retain their normal architecture

(c) Normocholesterolaemic (generalised abnormalities)

(i) Schuller Christian syndrome Eosinophilic granuloma of bone Letterer Siwe syndrome

(ii) Xanthoma cells in inflammatory and tumour tissues

(2) Gaucher s disease (generalised abnormalities)—Cerebroside abnormality (cerebrosiderosis)

(3) Niemann Pick s disease (generalised abnormalities)—Sphingomyelin abnormality (sphingomyelinosis)

It is seen at once that this very rough analysis of the principal types is divided according to the specific lipoid substance undergoing abnormal metabolism and storage Further it may be seen that only three of these clinico pathological variants should give rise to differential diagnostic problems in that their manifestations are widespread These are —

(1) The triad of Schuller Christian syndrome eosinophilic granuloma of bone and Letterer Siwe disease (non lipoid histiocytosis)

(2) Gaucher s disease

(3) Niemann Pick s disease

The first group originally regarded as being composed of separate entities is now believed to represent clinical variants of one basic lesion Thannhauser has suggested a single title of eosinophilic xanthomatous granuloma as a group title for the three conditions based on the pathological findings of Engelbreth Holm *et al* (1944) who demonstrated that the natural history of the condition fell into four phases —

(1) Proliferative—Histiocytic proliferation with some eosinophils but no foam cells

(2) Granulomatous—Increase of blood vessels reticulum cells and fibro blasts with eosinophils and giant cells (Touton cells)

(3) Xanthomatous—Accumulations of groups of foam cells

(4) Fibrous—Considered to be a healing phase

These four phases show no strict demarcation and it seems that eosino philic granuloma of bone is simply a monosymptomatic or early form of Schuller Christian s syndrome (Rowland 1928 1929) or lipoid granulomatosis as it has been designated by Chester (1930) and Frazer (1935)

The younger the individual the more rapid the course of this systemic disease thus Letterer Siwe disease—a very rare condition—is found in infants up to two years of age and pursues a rapidly fatal course occupying a period of weeks or a few months It is associated with fever and a generalised skin rash together with lymphadenopathy and hepatosplenomegaly Ulcerative lesions in the pharynx destructive lesions in bones and a progressive anaemia are associated features Histologically the lesions show similar appearances in all sites and are characterised by a proliferation of phagocytic cells which tend to be large and irregular in size with pale cytoplasm containing vacuoles and remnants of phagocytosed material Giant cells containing several nuclei may occasionally be seen



Fig 11 4
Sinus proliferation of lipoid containing cells in spleen (Gaucher s dis ase) (H and E ×50)



Fig 11 5
Pro iferation of stroma with infiltration of l poid conta ning cells in bone (Gaucher s disease) (H and E 110)

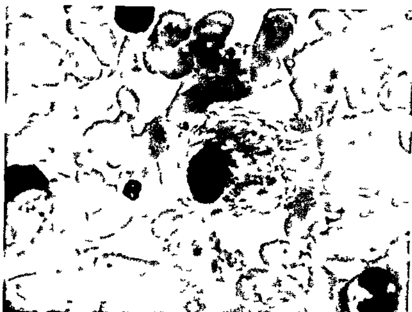


FIG 11 22
Gaucher s cell in peripheral blood Leishman s stain (× 1 000)



FIG 11 23
Sinus proliferation of lipoid containing cells in a lymph node (Gaucher s disease) (H and E × 110)

(a) REACTIVE CHANGES

The changes which result in the lymphoid tissue from reaction to injury seem to depend on two biological characteristics of the cells involved These are their phagocytic activity and their tendency to proliferate Although it is believed that the cells of the system are fundamentally alike in their origin yet it has been stated earlier that whereas many of the functions of the reticulum cell are recognised those of the lymphocyte are as yet only poorly understood

Non specific inflammatory reaction results in follicular hyperplasia and sinus catarrh in the acute and subacute phases and in fibrosis in the more chronic phases In all stages there is considerable cellular proliferation and some evidence of active phagocytosis in the cells produced

Follicular hyperplasia When this change occurs the follicles become very prominent showing the characteristics of Flemming s centres with pale actively dividing cells surrounded by a clear-cut rim of well-differentiated lymphocytes (Figs 11 26-28) Reticulin impregnation shows an absence of reticulin fibres within the follicles with clear-cut strands surrounding them (Fig 1 5) The active cellular division with frequent mitoses which occurs in the centre of the follicle may cause suspicion of malignancy if the condition is not recognised (Figs 11 29 32) Another feature which may give rise to difficulty is that the small vessels in the lymph nodes may show endothelial proliferation and on cut section may even mimic epithelial alveoli or the giant cells of Sternberg Reed type

Follicular hyperplasia is most frequently seen in the lymph nodes draining infected areas such as the tonsils or in the axilla and inguinal regions following sepsis in the arm or leg It may occur as a more or less isolated change in the node but frequently is associated with sinus catarrh

Sinus catarrh In this condition the reaction is manifested almost entirely by a proliferation of the reticulum cells lining sinuses These become distended and are filled by lakes of stagnant lymph and large cells of the reticulum series (Figs 11 33 39) some of which lie free in the sinuses Included among these are many showing active phagocytosis (Figs 11 40-41) Again mitoses are quite common and must not be confused with malignancy (Figs 11 42-43) Follicular hyperplasia and sinus catarrh are frequently seen together in the same lymph node but one or other change may predominate completely

The principal points of diagnostic significance in these conditions are —

(1) The realisation that a very considerable degree of cellular activity with numerous mitoses is the rule

(2) The differentiation of the pseudofollicles of follicular lymphoma from follicular hyperplasia This has already been discussed (Chapter 5)

(3) The recognition of a very cellular sinus catarrh from a carcinomatous invasion

(3) Proliferative Reactions of Lymphoid Tissue to Inflammatory Stimuli

The inflammatory reaction in general is a special protective mechanism against injurious agents which tends to be essentially aggressive in view of the activity of certain mobile cells which from the morphological point of view play an essential role in the defence reaction It has become clear however that chemical and physico-chemical aspects of inflammation are as important as the morphological changes It is the custom to consider inflammation to be of acute and chronic type The morphological appearances of these two varieties differ sharply for in the acute form the polymorpho nuclear leucocyte plays the chief role whereas in chronic inflammation the mononuclear cells both in the blood stream and in the tissues which have been identified in a previous section with the reticulum cell are pre-eminent *There are many other differences between acute and chronic inflammation* and one more must be mentioned here This is the tendency to fixed tissue proliferation in many chronic inflammatory changes a reaction which has been described as granulomatous This cellular proliferation may under certain circumstances be difficult to differentiate from true blastoma formation

Forbus (1943) has suggested that a more specific definition of granuloma should be used and has differentiated granulomatous chronic inflammation and the granulomatous change which may occur in the course of healing in an acute process from what he calls genuine granulomatous inflammation He has suggested that the granulomatous change in chronic inflammation is either a slow healing process following an acute inflammatory change or is a fixed tissue response to mild or repeated injuries by the same types of agents which normally produce acute and chronic inflammatory reactions In either case the granulomatous change is secondary to some preceding tissue damage A true granulomatous inflamma tion *on the other hand is described as being a primary process initiated* by a special group of harmful agents which through their stimulating or injurious effect bring into primary defensive activity a specialised cellular mechanism The mechanism to which the author refers is of course the reticulo-endothelial system

Whether or not it is considered necessary to make use of this rather sharp differentiation it does focus attention on that group of inflammatory conditions which most commonly give rise to difficulties in diagnosis from the primary tumours of lymphoid tissue

It is proposed to discuss the inflammatory reactions in lymphoid tissue under two headings —

(*a*) Reactive changes resulting from non specific irritative or noxious stimuli

(*b*) Certain specific inflammatory conditions of varying aetiology which produce changes which can be called granulomatous using the term in its broadest sense

(a) REACTIVE CHANGES

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In the more chronic phases of non specific inflammatory reaction in the lymph nodes fibrosis occurs

Fibrosis At first hyalinisation (Fig 11 38) in the sinuses and later active fibrosis may occur so that a lymph node which has previously been the site of an inflammatory process may become hard and show considerable fibrous infiltration (Figs 11 44-46) If any areas of normal lymph tissue remain it will be obvious that the fibrosis is replacing sinus areas but in advanced cases architectural upset may occur and cause confusion more particularly with those cases of Hodgkin s disease showing fibrosis The absence of typical tumour cell proliferation should in most cases make the diagnosis clear but it is seen why it is of such importance to avoid selecting for biopsy a lymph node which might be the site of chronic inflammatory change

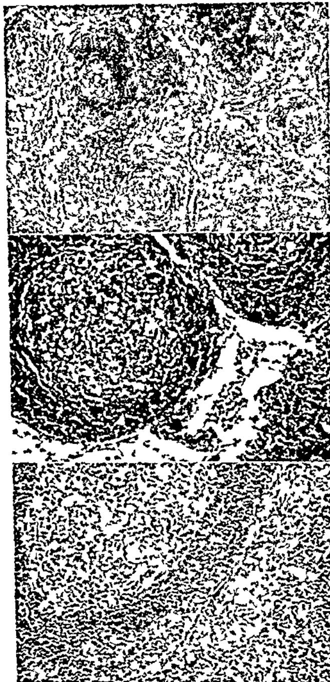


FIG 11 6

Prominent germinal folli les in a lymph node draining a non specific inflammatory area (H and E ?3)

FIGS 11 7 and 11 8

Cellular structure of germinal follicles showing pale actively proliferat ng central cells with a rim of more darkly staining fully differentiated lymphocytes From a case of infectious mononucleosis (H and E ×100)

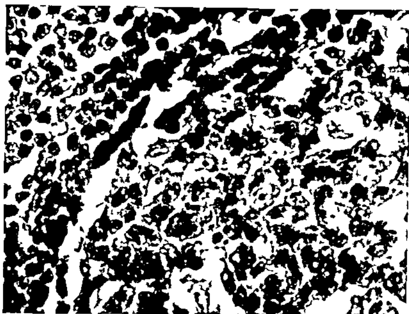


FIG 11 29

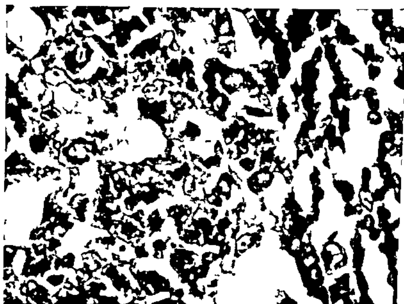


FIG 11 30

FIGS 11 29 and 11 30

Junction of central and peripheral part of germinal follicles showing larger paler cells centrally and small well formed lymphocytes peripherally (H and E ×450)

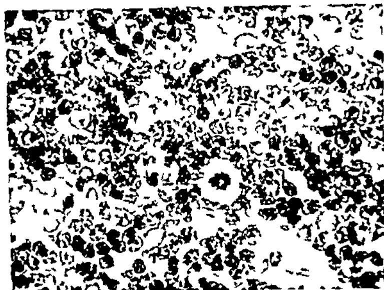


FIG 11 31

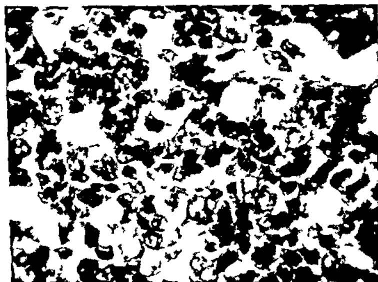


FIG 11 3_

FIGS 11 31 and 11 3

Cellular activity in the centre of a germinal follicle includin mitotic figures (H and E ×450)

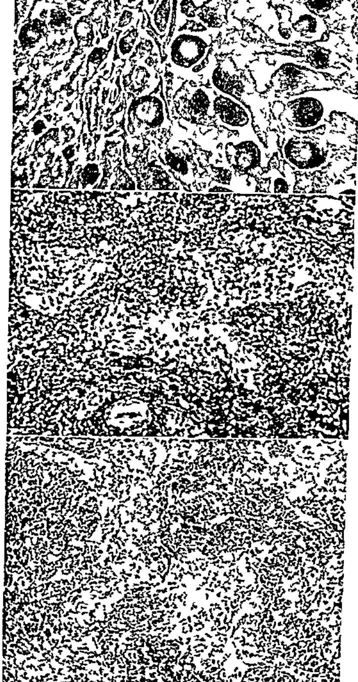


FIG 11 33

Mesenteric lymph node from a case of Crohn's disease (regional ileitis) showing gross sinus distension throwing the follicles into relief (H and E × 3)

FIG 11 34

Proliferation of large pale cells in the sinuses from a case of Brucellosis (H and E × 100)

FIG 11 35

Well marked sinus proliferation from a case of secondary syphilis (H and E × 100)



FIG 11 36
Sinus proliferation with commencing hyalinisation from a lymph node in the axilla draining carcinoma of the breast showing no evidence of metastasis (H and E ×110)



FIG 11 37
Sinus proliferation in an inguinal gland from a case of septic foot The capsule of the lymph node and some cell distension of peripheral sinuses can be seen in this section (H and E ×110)



FIG 11 38
Sinus proliferation showing hyalinisation from a case of non specific inflammatory reaction in a cervical lymph node (H and E × 110)

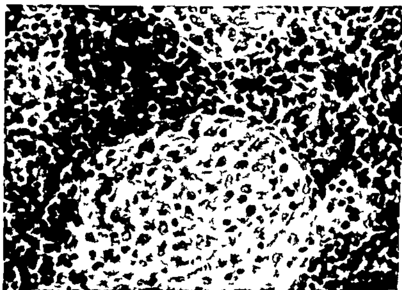


FIG 11 39
Proliferating cells in a sinus standing out in marked contrast from the surrounding lymphocytes from a case of carcinoma of the breast with no metastasis in axillary gland (H and E × 450)



FIG 11 40
Active phagocytosis by a macrophage cell in a sinus (H and E ×450)



FIG 11 41
Large phagocytic cell in lymph node sinus engulfing an erythrocyte (H and E ×1 000)

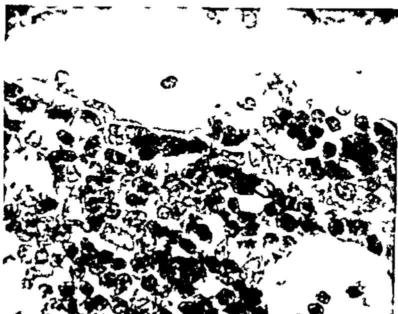


FIG 11 42
Cellular proliferation of lining cells in a sinus (H and E ×450)

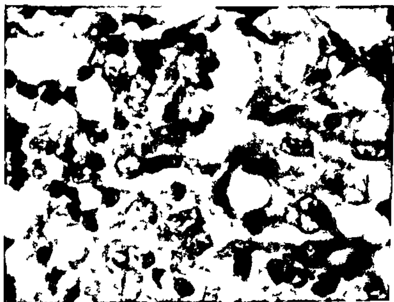


FIG 11 43
Cellular activity among the cells proliferating in a sinus (H and E ×450)

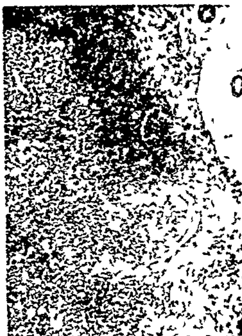


FIG. 11 44



FIG 11 45

FIG 11 44

Peripheral subcapsular fibrosis with some sinus proliferation showing follicle remnants A cervical lymph node in a case of non-specific inflammatory reaction (H and E × 100)

FIG 11 45

Dense fibrosis with follicular remnants from a case of non-specific inflammatory reaction An inguinal lymph nod (H and E. 100)



FIG 11 46

Dense fibrosis completely replacing normal architecture from a case of non specific inflammatory reaction (H and E. × 100)

(*b*) SPECIFIC INFLAMMATORY LESIONS

Under this heading will be discussed *certain inflammatory* conditions which have more commonly been reported as causing diagnostic difficulty in relation to tumours of lymphoid tissue Sarcoidosis is included in this group *not because* its specific inflammatory origin is considered proven but because its cellular reaction is essentially of the same type as the other conditions described in this section

It is clear that no discussion such as the one which follows can be complete and for this reason only conditions of genuine differential diagnostic difficulty are included For instance no mention is made of *syphilis* as it is considered that it is a disease where specific diagnostic tests can be applied and where the pathology is characteristic In the same way certain infectious *disorders of viral origin such as mumps and measles which produce* proliferative changes in lymphoid tissue are omitted as their other manifestations make their diagnosis clear

The following conditions will be discussed —

Infectious mononucleosis (glandular fever)
Brucellosis
Torulosis
Histoplasmosis
Trypanosomiasis
Visceral Leishmaniasis (Kala Azar)
Tuberculosis
Sarcoidosis

It may be noted that in the majority of the conditions to be discussed in the following group the lymphoid tissue tumour with which confusion is *likely to arise is Hodgkin s disease This is largely because in many* inflammatory conditions the reticulum cell elements proliferate and become enlarged with the infrequent appearance of binucleated forms This proliferation will be found on close examination to be of sinus *origin In* short therefore the demonstration of an isolated abnormally large reticulum cell superficially resembling the type described by Sternberg and Reed does not necessarily indicate Hodgkin s disease

Follicular hyperplasia and sinus proliferation and catarrh are therefore the changes which occur in lymphoid tissue as a result of inflammatory stimulus These changes are purely non specific and very frequently it is not possible to define the exact organismal or other cause by histological means but only by more specialised tests

It is however a common diagnostic problem to be faced with biopsy material from a lymph node and then it is of the utmost importance to *distinguish an inflammatory* process from one of primary neoplastic origin

Infectious mononucleosis This disease originally described by Pfeiffer in 1889 under the title of glandular fever is an acute infectious process which occurs sporadically and *sometimes in epidemics It is associated with fever*

and prostration together with a generalised lymphodenopathy and hepato splenomegaly and the appearances in the peripheral blood of abnormal cells which bear some resemblances both to the lymphoid and the mononuclear series Skin rashes sore throat and gastro intestinal upsets are common findings It is seen how a process of such widespread manifestations might cause confusion with tumours of lymphoid tissue The finding of the abnormal cells in the blood together with certain heterophile antibodies detected by the test devised by Paul and Bunnell (1932) should make the diagnosis clear but occasionally a biopsy may be performed on an enlarged lymph node before these signs become positive Since the disease is rarely if ever fatal material for study is necessarily strictly limited

The changes found in the lymph nodes in infectious mononucleosis should not cause confusion with tumours of lymphoid tissue There is a marked follicular hyperplasia of the type already described with the production of well-defined germinal centres (Figs 11 27 30) It has been suggested (Downey and Stasney 1935) that the abnormal lymphoid cells found in the peripheral blood during the early stages of the disease may be produced in these hyperplastic follicles There is frequently some associated sinus proliferation in the nodes with the appearance of large cells closely resembling reticulum cells and of the type found in the peripheral blood during the later stages of illness

In the few cases which have been examined at post mortem a generalised reticulo-endothelial hyperplasia of lymph nodes and spleen has been demonstrated together with an excess of large mononuclear cells in the bone marrow These changes are the result of a reaction of the lymphoid tissues to an infectious agent probably of viral origin and are of particular interest in that not only is there apparent the usual cellular proliferation which occurs in all cases of injury to this tissue but also there is an invasion of the circulating blood by cells produced in all probability from the germinal follicles and also from the reticulum cells of the sinuses

Brucellosis Brucellosis is a disease of widespread distribution producing a chronic form of fever showing a periodic rise and fall and therefore known as undulant fever It is associated with general malaise and aching pains in the joints and is produced by the three forms of Brucella—melitensis abortus and suis—specific agglutinins for which can be demonstrated in the serum of affected patients The disease is usually generalised and a frequent finding is a lymphadenopathy with or without hepatosplenomegaly For this reason a lymph node biopsy may well be performed before a recognisable agglutinin titre in the blood has made the diagnosis clear

Three main varieties of the disease have been described by Forbus (1943)

(1) The septicaemic or relatively acute type

(2) The focal variety also of acute nature

(3) The chronic type with a prolonged course

In the first two varieties the changes in the lymph nodes are slight and take the form of a sinus proliferation of the usual type and should not give

rise to any difficulty in distinction from tumours of lymphoid tissue In the third type however some more interesting observations have to be made for *it is in this variety that lymph node enlargement* together with an increase in size of the liver and spleen form an important symptom complex When it is added that skin irritations and infiltrations are common it may be realised *that a differential* diagnosis from one of the tumours of lymphoid tissue and in particular from Hodgkin s disease becomes a real difficulty The lymph nodes in these cases show a sinus proliferation of large monocytic cells but in addition to these changes areas of necrosis with subsequent hyalinisation and fibrosis as well as a proliferation of giant cells said closely to resemble Sternberg Reed cells have been described in occasional cases by Forbus and certain workers in his laboratory (Menefee and Poston 1938 Parsons and Poston 1939)

These workers have gone so far as to say that the changes which they observed in the lymph nodes of one case were typical of Hodgkin s disease and therefore speculated on the possible association of Brucellosis with Hodgkin s disease No case has been observed personally where there has been such close resemblance between the conditions but in those cases of Brucellosis where lymph nodes have been examined sinus proliferation has been a marked feature (Fig 11 34) Clearly much more evidence is required before any final assessment of this work can be made

Torulosis Torulosis is usually considered to be a rare condition produced *by one of the many yeast like Fungi Imperfecti known as Cryptococcus* hominis and for this reason is frequently known as Cryptococcosis

Zenker in 1861 described a condition which is almost certainly Torulosis and in *1894* and *1895* Busse described both *the disease and the organism* In recent years numerous reports have appeared in America and Australia and in a recent monograph Cox and Tolhurst (1946) point out that in Southern Australia the process can no longer be regarded as a rarity They estimate that 120 cases have been recorded in the world literature

The disease is of importance since in its commonest form it is almost invariably fatal The route of entry of the fungus is probably through the mucous membrane of the gastro intestinal and respiratory tracts but there is no concrete evidence of this nor is there any knowledge of an intermediate host

The organism shows a marked tendency to localisation in the central nervous system (the brain) and in the lungs In the great majority of cases the disease takes the form of a meningitis or meningo-encephalitis of acute or subacute form It may closely resemble tuberculous meningitis a condition with which it is readily confused clinically and the diagnosis must be made by the demonstration of the fungus in the cerebro spinal fluid

Cox and Tolhurst report that in more than 50 per cent of their cases lung lesions were present in addition to the meningitis and in 15 per cent of cases enlarged lymph nodes have been noted

It is this last pathological change which is of importance in relation to tumours of lymphoid tissue more particularly because there are several reports in the literature of cases of proved Torulosis where lymph node changes showed what were regarded as appearances typical of Hodgkin s disease

Cox and Tolhurst describe such a case (No 7 in their series) where evidence of the fungus could be found in the central nervous system and the lungs but not in the lymph nodes which were found enlarged at post mortem in the mesenteric para aortic and retroperitonial groups which had directly involved the cysterna chyli Enlarged glands were also found in the axillary cervical and inguinal regions

An examination of the lymph nodes was made by Professor R A Willis whose opinion was that the histological findings along with the gross morbid anatomy in this case are typical of Hodgkin s disease

Other reports with a direct bearing on this problem have been made by Freeman and Weidman (1923) Smith and Crawford (1930) Fitchett and Weidman (1934) Wile (1935) Magruder (1939) Heine *et al* (1940) and Warvi and Rawson (1942) All these reports together with an unpublished account made at the Massachusetts General Hospital in 1934 by Dr T B Mallory have been fully reviewed by Cox and Tolhurst and one must agree with their interpretation of the results that no very conclusive evidence of Hodgkin s disease is presented in view of somewhat inadequate details in all these cases

The only case where the histological evidence of Hodgkin s disease is clearly stated is No 7 of the Cox and Tolhurst series described by Professor R A Willis

An analysis of the situation indicates therefore that a number of authors have suggested that the changes which occur in the lymph nodes in cases of Torulosis may on occasion present a picture capable of confusion with Hodgkin s disease Cox and Tolhurst have gone so far as to speculate in their case No 7 as to whether the appearances represent a coincidental finding of Hodgkin s disease in a case of Torulosis in the same way that the disease may be associated with tuberculosis or whether the changes are a manifestation of the fungus infection closely mimicking the appearances of the primary tumour of lymphoid tissue

In this connection it is of interest to note that Forbus states that he has repeatedly failed to grow any form of fungus from lymph nodes affected by Hodgkin s disease

In view of the fact that no case of Torulosis with lymphadenopathy had been seen personally I approached Dr J W Whittick at the Royal Cancer Hospital in London who has recently reported such a case to the Pathological Society of Great Britain and Ireland (Galton and Whittick 1951) and I am greatly indebted to him for his permission to study his material and to take the photomicrographs which appear in Figures 11 47 55 The following is a summary of the clinical history from this case

Male aged twenty years was admitted to the Royal Cancer Hospital on 15 12 49 complaining of moist scaling of the skin of the scalp forehead neck and trunk for a period of sixteen months In addition he had suffered from malaise lassitude and heavy night sweats with some loss of weight

Six months previously swellings had developed in the left axilla which broke down and discharged thick yellow pus Enlarged lymph nodes in the left posterior triangle of the neck appeared and a biopsy—the specimen of which was not available—was reported as showing non specific chronic inflammatory changes

Serological tests for syphilis gonorrhoea Salmonellas and Brucella were all negative Paul Bunnell test was negative and sternal marrow showed a non specific rise in leuco myeloid elements

During the previous two and a half years the patient had served in the Merchant Navy in North America Iraq and the Red Sea as well as visiting numerous European countries He had suffered no illnesses at this time

On examination in hospital the patient was thin but well nourished and showed numerous scattered skin lesions all over the body varying in size from a few centimetres to 10 12 cm across Some of these were moist scaling erythematous patches with varying degrees of crusting whilst others were dry and scaling Enlarged discrete rubbery lymph nodes were palpated in both sides of the neck both axillae and in the left epitrochlear region The spleen was palpable 5 cm below the costal margin

After two weeks in hospital his general condition improved and he gained a little weight but despite radiotherapy to the skin the lesions there showed no improvement

In May 1950 a biopsy was taken from the right axilla which showed some what equivocal changes and a tentative diagnosis of Hodgkin s disease was made Radio active phosphorus therapy was given with considerable improve ment of the skin lesions but the lymph nodes and spleen remained unaltered The patient was discharged but in August 1950 he became very ill and was admitted to another hospital where he complained of headache neck rigidity and cranial nerve palsies He deteriorated rapidly and died on September 15 1950 A post mortem was performed and the fungus of Cryptococcus hominis was demonstrated as spores in the liver spleen suprarenals lung and lymph nodes

It is with the lymph node changes that we are concerned here and their examination reveals the following features —

The lymph node taken for biopsy in May 1950 shows a greatly enlarged gland with considerable fibrosis in and around its capsule but in the peripheral areas normal follicular pattern remains with some evidence of distension and cellular proliferation in sinuses (Figs 11 47 49) The normal fibrous trabeculae are accentuated and there is considerable hyalinisation and patchy fibrosis in the sinuses throughout the node (Figs 11 52 11 53) In some areas this fibrosis is so intense as to produce zones of whorling made up of acellular collagen *Blood vessels throughout the lymph node show*

endothelial proliferation and there is a tendency for fibrosis to be more marked around the vessels

Scattered in an irregular manner through the lymph node but usually clearly demonstrable in sinuses are large pale cells which have the general characteristics of reticulum cells (Figs 11 50 11 51) They occur occasionally singly but usually in clumps Cytoplasm is extremely granular and sometimes contains vacuoles—features not associated with Hodgkin s disease The vast majority of these cells contain a single sometimes convoluted nucleus but occasionally cells with two nuclei are seen No multinucleate varieties are discovered and mitoses are not a feature No spores or yeast like organisms are demonstrable in this section The lymph nodes removed at post mortem show occasional yeast like spores particularly in the peripheral sinuses sometimes intracellular and sometimes lying free (Figs 11 54 11 55) There is a generalised hyalinisation and fibrosis which tends to upset the normal architecture but the enlarged reticulum cells are not such a marked feature as in the original biopsy The appearances in liver and spleen are somewhat similar showing accumulations of round cells with zones of fibrosis among which spores can be demonstrated

It would appear therefore that in about 15 per cent of cases of Torulosis lymphadenopathy may occur and that in a small number of these cases—probably 4 5 per cent of the total number—a proliferation of reticulum cells can give rise to some confusion in diagnosis Careful search for the fungus is of importance both by staining methods and by culture but it is certainly possible to see lymph nodes in Torulosis where it is not possible to demonstrate the organism

The course of the disease in most cases should not cause confusion for whereas meningitis is very common in Torulosis it is virtually non-existent in Hodgkin s disease

To summarise therefore this is a rare condition which in about 5 per cent of its cases may present a differential diagnostic problem of some difficulty It is important to recognise this fact for the readily available travel facilities between those areas in the world where its occurrence is not so uncommon make the possibility of its appearance more likely than in the past

Histoplasmosis This is a rare condition which is caused by one of the fungi imperfecti Histoplasma Capsulatum The organism was described by Darling in 1908 when examining cases of Kala Azar and first cultured from infected tissues by Hansmann and Schenken (1933) and De Monbreun (1934) It attacks the body tissues in a manner somewhat similar to visceral Leishmaniasis by affecting principaly the reticulo-endothelial system It is for this reason that confusion in diagnosis may arise between Histoplasmosis and the primary tumours of lymphoid tissue

At first thought to be a tropical disease the majority of cases of this condition have been reported in the United States of America but it would

FIG 11 47 FIG 11 48

FIGS 11 47 and 11 48

Sinus proliferation resembling sinus catarrh showing large pale cells in a case of Torulosis (H and E ×110)



FIG 11 49

Remaining normal follicle (Torulosis) (H and E × 110)

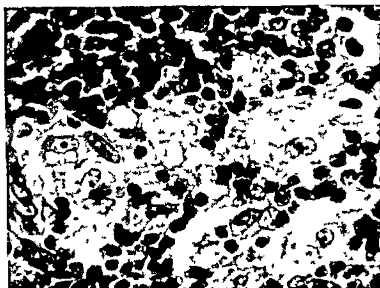


FIG 11 50

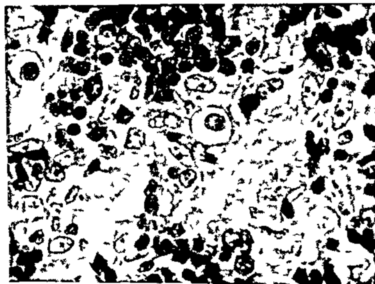


FIG 11 51

FIGS 11 50 and 11 51
Proliferating sinus cells showing pale foamy [illegible] in [illegible]
(H and E × 400)

FIG 11 47

FIG 11 48

FIGS 11 47 and 11 48
Sinus proliferation resembling sinus catarrh showing large pale cells in a case of Torulosis (H and E × 110)



FIG 11 49
Remaining normal follicle (Torulosis) (H and E × 110)

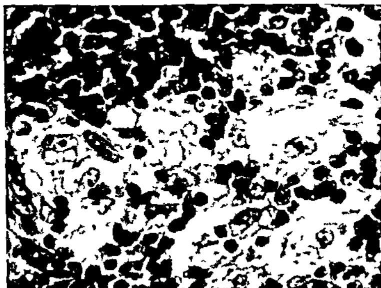


FIG 11 50

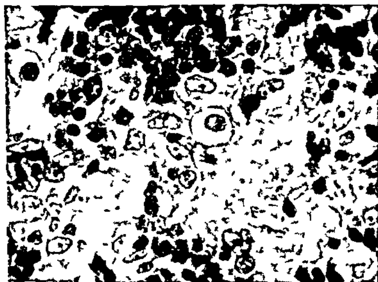


FIG 11 51

FIGS 11 50 and 11 51
Proliferating sinus cells showing pale foamy cytoplasm in Torulosis
(H and E ×450)

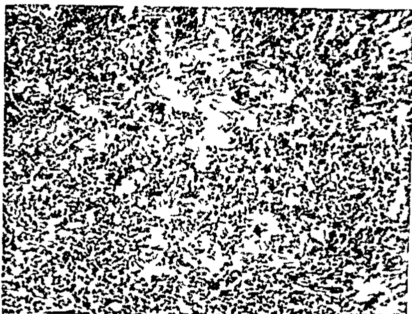


Fig 11 52



Fig 11 53

Figs 11 52 and 11 53
Hyalinisation and fibrosis in the sinuses in Torulosis (H and E × 110)

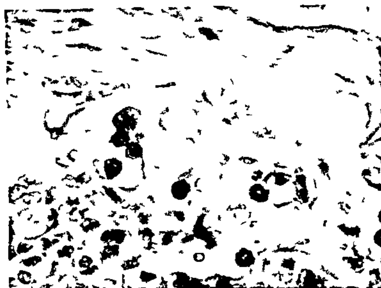


FIG 11 54

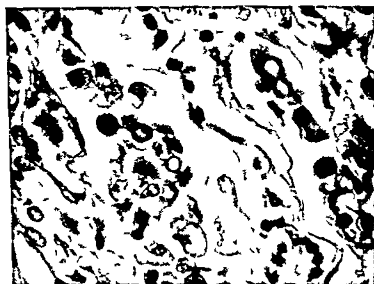


FIG 11 55

FIGS 11 54 and 11 55

Spores of torulae lying in the sinuses some of which are intracellular and some extracellular (Mucicarmine stain × 450)

appear that distribution is world wide cases having been described particularly in South Africa (Simpson and Barnetson 1942)

All age groups are affected by this disease but it is particularly common among young children As many cases are reported during the first year of life as in any decade

The mouth would appear to be the portal of entry of the organism which attacks the entire reticulo endothelial system becoming localised in the liver spleen and bone marrow Lymphadenopathy is a common feature In some examples of the condition localised affections of the skin and lungs have been described

The disease tends to be of a chronic nature the most important clinical features being fever malaise loss of weight and chronic cough The commonest physical signs are focal consolidation of the lungs splenomegaly and lymphadenopathy

The pathological changes in the tissues are dependant on the affinity of the organism for the reticulo-endothelial cells where it exists as an intracellular parasite in much the same way as the malarial parasite lives in the erythrocyte Forbus has suggested that there may be an essential difference between these two diseases in that the red cell acts in a completely passive role in malaria whereas it is probable that the reticulum cells actively engulf the parasite in histoplasmosis

Histoplasma capsulatum stimulates the proliferation of reticulum cells throughout the system and in the lymph nodes where the changes may cause confusion with primary tumours the picture is essentially a sinus proliferation of large mononuclear cells of reticulum type the cytoplasm of which can be seen to contain large numbers of small parasites most readily stained by the periodic acid Schiff method (Lillie 1948)

Foci of necrosis are commonly seen which may in some cases have the appearance of caseation and in the most chronic examples patchy calcification may occur The photomicrographs illustrating this condition (Figs 11 56 58) were prepared from material kindly loaned by Dr G J Cunningham from a case reported by Cunningham and Garrod (1951)

Trypanosomiasis Trypanosomiasis is usually described as existing in three forms Two varieties occurring in Africa the Gambian type produced by trypanosoma gambiense and the Rhodesian type produced by trypanosoma rhodesiense and the third variety existing in South America *(Chagas Disease)* of which the causative agent is trypanosoma cruzi

In both the African forms transmission of the parasite from man to man is by the bite of the tsetse fly (Glossina palpalis and tachenoides) The organism is capable of reproduction in the human and so far as is known retains its trypaniform structure throughout its life cycle in man

The morphology of the organism in man and the clinical course of the disease is essentially similar in both African forms except that trypanosoma rhodesiense is more virulent and more resistant to treatment The demon

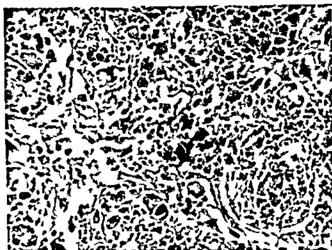


FIG 11 56

Proliferation of large cells with foamy cytoplasm in the sinuses in histoplasmosis (H and E × 100)

FIG 11 57

FIG 11 58

FIGS 11 57 and 11 58

Giant cells lying in the sinuses containing large numbers of histoplasmosis spores in the cytoplasm (Picro Mallory stain × 405)

stration of the organism usually in the peripheral blood provides the diagnosis of the disease

The disease may follow one of three types of course —

(1) Chronic course of several years with few or no evidences of disease except changes in cerebrospinal fluid

(2) Cases with an acute early stage of two to three weeks characterised by fever enlarged lymph nodes xanthematous eruptions and transient oedemas which passes into a chronic encephalitic stage The whole course of the disease in this form lasts about one year

(3) A very acute course with death occurring within a few months and with no signs of encephalitis

The pathology of this African form of trypanosomiasis is characterised by a chronic meningo encephalitis and lymphadenitis Glands in the posterior triangle of the neck and the axilla and inguinal regions are most commonly affected

The lymph nodes are usually enlarged and rubbery with a pinkish fleshy appearance on cut surface whilst in the later phases of the disease they become hard and fibrous Histologically the change is produced by a sinus proliferation with enlargement and hyperplasia of reticulum cells In the more chronic stages of disease hyalinisation and later fibrosis occurs in the sinuses which may progress to destroy normal architecture It is this lymph node change which may cause confusion in diagnosis with primary tumours of lymphoid tissue and in particular with Hodgkin s disease In the more *chronic forms of trypanosomiasis a lymph node biopsy may be performed* as a diagnostic measure

A case of Gambian trypanosomiasis has been seen at autopsy at West minster Hospital which had been diagnosed as Hodgkin s disease elsewhere during life as a result of lymph node biopsy The lymph nodes examined from the post mortem material showed the changes already described of sinus proliferation with enlarged reticulum cells but with no intrinsic architectural destruction and none of the other features of Hodgkin s disease such as multi nucleate giant cells These appearances should not give rise to any serious difficulties of diagnosis (Figs 11 59 60)

South American trypanosomiasis (Chagas disease) is transmitted from man to man by bug bites (chiefly Triatoma megista) The parasite exists in the blood as a typical trypanosome the demonstration of which provides the diagnosis of the disease but unlike the African type parasite it is incapable of reproducing itself in the blood and invades the tissues where it is converted into typical *leishmania like parasites to produce lesions in many* ways similar to those which occur in Visceral leishmaniasis This form of disease also occurs in an acute and chronic form but lymphadenopathy is not such a common feature and differential diagnosis from primary tumours of lymphoid tissue can hardly be said to arise



FIG 11 59
Subcapsular fibrosis with remnant of a normal follicle beneath it in a case of *trypanosomiasis*
(H and E 110)

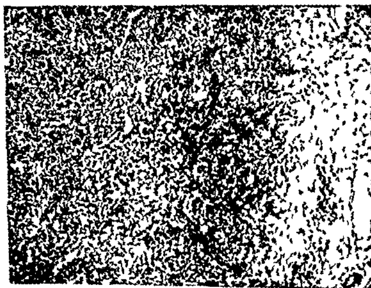


FIG 11 60
Fibrosis associated with an area of *normal lymphoid tissue* in trypanosomiasis
(H and E 110)

Visceral Leishmaniasis (Kala Azar) This infectious disease characterised by enlargement of the spleen and usually of the liver together with long continued irregular fever anaemia and leukopenia with progressive loss of weight and strength is caused by a protozoon parasite Leishmania donovani which is present in the spleen liver peripheral blood and cells of the reticulo-endothelial system The diagnosis of the condition depends on the demonstration of the causative organism in the form of leishmania bodies in the cytoplasm of the reticulum cells throughout the body The changes produced in lymph nodes as elsewhere is a sinus proliferation of reticulum cells and no great difficulty should arise in differential diagnosis from primary tumours of lymphoid tissue



Fig 11 61
Large mass of lymph nodes from the axilla showing caseation on cut surface in a case of senile tuberculosis which had resembled clinically a lymphosarcomatous mass

Tuberculosis Tuberculosis as a differential diagnosis from primary tumours of lymphoid tissue is a problem chiefly of clinical significance associated with the disease when it manifests itself as a lymph node enlargement particularly in the neck On these occasions the rubbery isolated nature of the glands enlarged by lymphoid tumours help to differentiate from those affected by the inflammatory process which tend to become matted together In a number of cases however a lymph node is removed for biopsy before the condition can be diagnosed with certainty (Fig 11 61) The histological appearance of the tuberculous gland is of course quite characteristic and the sinus proliferations of endotheliod and giant (Langhan s) cells with central caseation and sometimes demonstrable tubercle bacilli need no further discussion here

Sarcoidosis Sarcoidosis was first recognised as a generalised systemic disease by Schaumann who presented his views on this subject as a thesis for the Zambuco prize in Paris in 1914 The skin lesions had previously been described by Besnier in 1889 under the title of Lupus pernio and by Boeck in 1899 who studied the microscopic appearances and introduced the term sarcoid

Confusion of terminology in this condition has resulted from the fact that a number of syndromes have appeared as apparently separate entities yet

which represent only localised affections of different anatomical areas by the same underlying process Thus the skin manifestations are associated with the names of Besnier and Boeck and the titles lupus pernio and sarcoid Bone involvement of toes and digits originally described by Jungling in 1919 as osteitis tuberculosa multiplex cystica and the uveoparotitis of Heerfordt (1909) are further examples of manifestations of the same process which bear separate titles

This condition provides an important differential diagnostic problem from the tumours of lymphoid tissue because although a disease of widespread manifestation it affects principally the lymph nodes and very frequently presents clinically as a mass in the neck or mediastinum It pursues a benign course and out of a series of twenty two cases autopsied by Ricker and Clark (1949) in only three could death be attributed directly to the disease One example has been seen of a case coming to autopsy at Westminster Hospital and on this occasion death had followed a widespread bronchopneumonia developing where enlargement of mediastinal lymph nodes had given rise to lung collapse Following the work of Ricker and Clark and of Scadding (1950) it seems necessary to accept a histological definition in this condition for aetiology remains obscure

The process develops as tubercle like areas composed of epithelioid cells surrounded by a rim of lymphocytes and giant cells containing peripherally situated nuclei sometimes of Langhan s type and sometimes resembling foreign body giant cells (Figs 11 62 66) The proliferating zone is sharply demarcated by reticulin fibres but shows little or no reticulin within the cellular area (Fig 11 67) Caseation is never seen but occasionally fibrinoid necrosis can be demonstrated (Figs 11 63 11 64 and 11 68) Inclusions are found in the giant cells in many cases which may be of two varieties the so-called asteroids of Wolbach (1911) (Fig 11 69) or the basophilic masses described by Schaumann (1941)

Areas affected by this disease other than the lymphatic system are the liver spleen lungs skin and bone marrow particularly in the bones of the fingers and toes The eye in iridocyclitis and the salivary and lachrimal glands also may be involved

In view of the histological appearances tuberculosis has frequently been incriminated as the cause of sarcoidosis but although it cannot entirely be excluded no conclusive evidence exists to prove its association Ziegler (1881 1885) described a condition which he called large celled indurative hyperplasia in which he claimed to have found tubercle bacilli but although this condition appears to have been sarcoidosis no conclusive evidence to prove the association of these two conditions has been produced in more recent years Evidence against the tubercle bacillus as an aetiological factor has been given by Longcope and Pierson (1937)

The differential diagnosis of this condition from the various tumours of lymphoid tissue is clear cut if biopsy material is available for examination

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The differential diagnosis of this condition from the various tumours of lymphoid tissue is clear cut if biopsy material is available for examination

In lymph nodes it occurs as a sinus proliferation compressing the surrounding normal architecture

Two other conditions which closely resemble sarcoidosis may be mentioned here for their histological appearances are so similar as to provide a common differential diagnostic problem They are Stengel Wolbach sclerosis and Crohn s disease or cicatrising entero-colitis The former is an ill-defined process which closely resembles sarcoidosis in its histological manifestations Although certain authors (Robb Smith 1938 Fowler 1948) have maintained its individuality there does not seem to be sufficient evidence for such a differentiation and it would appear to be merely a manifestation of the same disease process

Crohn's disease is a more complicated problem It is a cicatrising condition which may affect any part of the bowel although characteristically the terminal ileum is involved (Crohn *et al* 1932) Accumulations of round cells of lymphocytic type are found in the bowel wall together with proliferation of giant cell systems of the type seen in sarcoidosis Caseation is not a feature and tubercle bacilli cannot be found

Where round cell proliferation predominates it may sometimes be necessary to differentiate this condition from lymphosarcoma affecting the bowel but the differences both clinically and pathologically are usually quite clear cut



Fig 11 6[illegible]
Gross sinus proliferation without caseation in a lymph node from a case of sarcoidosis (H and E × [illegible]5)



Fig 11 63
Sinus proliferation showing clear demarcation from lymphoid tissue without caseation in sarcoidosis (H and E × 110)



FIG 11 64
Sinus proliferation showing clear demarcation from lymphoid tissue without caseation in sarcoidosis (H and E × 110)



FIG 11 65
Proliferation of cells in sinuses including giant cells in sarcoidosis (H and E × 110)

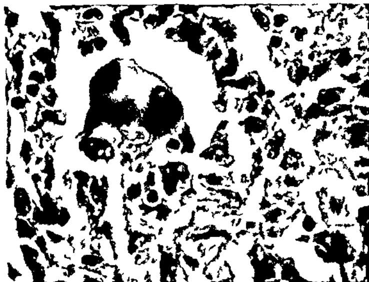


FIG 11 66
Multinucleate giant cell (sarcoidosis) (H and E ×450)

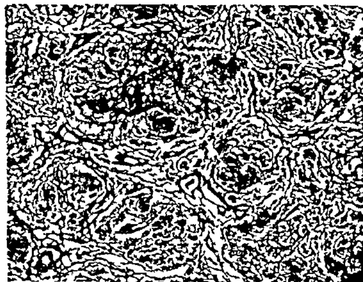


FIG 11 67
Gomori's reticulin impregnation in sarcoidosis (×110)

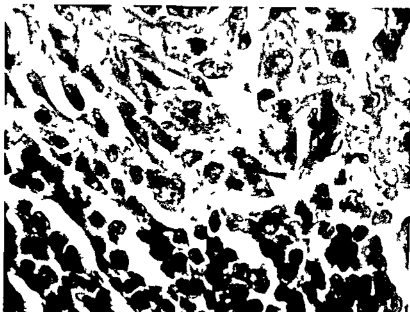


FIG 11 68
Junction of cells proliferating in sinuses with lymphoid tissue in sarcoidosis (H and E ×450)

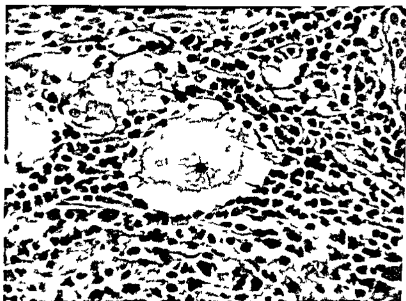


FIG 11 69
"Asteroid" body in giant cell in a case of sarcoidosis (H and E ×450)

CHAPTER 12

EFFECTS OF THERAPY ON PRIMARY TUMOURS OF LYMPHOID TISSUE

THE methods of therapy employed in treating the primary tumours of lymphoid tissue will be considered under the following headings —

(1) Surgery

(2) Irradiation and the use of radio-active materials

(3) Chemotherapy

Various methods of treatment by vaccines and sera will not be discussed here They have been used mainly by those who believed some specific inflam matory agent to be the cause of the condition and have been applied in particular to Hodgkin s disease Certain constitutional improvements have been reported but there is no convincing evidence of any real therapeutic benefit having been achieved

Surgery

The use of surgery in the treatment of these tumours always plays a part in that a biopsy must be performed in order to establish a diagnosis

Certain authors have suggested that patients with localised disease involving accessible glands should be given the benefit of radical removal There are examples in the literature where cases of this type have survived for long periods after such treatment (Slaughter and Craver 1942) The difficulties of deciding whether or not a particular patient is in fact presenting a localised form of disease have already been discussed and attention has been drawn to the fact that affected glands in inaccessible sites may in fact pass unnoticed Although reports of good results are extremely rare it is felt that in a disease group where prognosis is so bad there is some justification for radical removal of apparently isolated gland groups In a case already mentioned (Case No 17) good results have followed this form of treatment

Irradiation and the Use of Radio Active Materials

Irradiation by means of high voltage X rays is the principal weapon in the treatment of the primary tumours of lymphoid tissue Certain radio active isotopes including radio-active phosphorus colloidal manganese and colloidal gamma ferric oxide have been used in recent years but the results of these trials are as yet disappointing

Primary lymphoid tissue tumours are for the most part radiosensitive which might be expected of a group arising from cells belonging to a system which in its normal state is rapidly destroyed by irradiation The lymphocytes are among the most actively growing cells in the body and are very sensitive

to irradiation (Fox and Farley 1923 Minot and Spurling 1924) It has been found impossible however to give a dose sufficient to destroy completely all normal lymphoid tissue without seriously damaging other tissues (Hughes and Job 1937) Fox and Farley have shown that small doses of irradiation tend to produce a lymphocytosis whilst larger doses depress the number of lymphocytes

The effects of irradiation on the lymphoid tissue tumours may be summarised as follows —

In the more rapidly proliferative lesions such as lymphosarcoma reticulum cell sarcoma and anaplastic sarcomas apparent complete disappearance of tumour substance may follow irradiation A good example of this is seen in Case No 4 (Figs 6 18 and 6 19) The large ulcerating lesion in the throat showed typical appearances of lymphosarcoma at biopsy but the mass disappeared completely following treatment At autopsy no evidence of remaining tumour cells or any other abnormality could be found at the primary site although widespread involvement of other organs had occurred No evidence of fibrosis or stromal change of any sort could be discovered Similar results have been observed in other cases in relation to lymph nodes and other areas affected by tumour proliferation Sometimes zones of necrosis are seen following irradiation but it is always difficult to be certain whether such a change represents the direct results of irradiation or whether it is merely a manifestation of the disease process

In Hodgkin s disease and the more benign tumours of lymphoid tissue the effects of irradiation are more difficult to assess It is common to see a biopsy before irradiation has commenced but only rarely is more material available before autopsy Less frequently than among the more rapidly proliferative tumours already described tumour masses may disappear completely following therapy but the most common changes which have been attributed to irradiation are areas of fibrosis and necrosis together with diminution in size rather than actual disappearance of tumour masses Foci of necrosis are quite commonly seen surrounded by reticulum cells the origin of which in some cases may be difficult to establish Fibrosis may be preceded by a diffuse hyalinisation but more frequently areas of accellular collagen are seen tending to produce whorls It is at once apparent that fibrosis in Hodgkin s disease is a normal feature of the condition and it may be difficult to estimate in any particular specimen whether a focus of fibrosis represents irradiation effect or whether it is a manifestation of previous chronic inflammatory change or simply a stage in the natural development of the disease Undoubtedly examples of intense fibrosis are seen in cases of Hodgkin s disease (Rosenthal 1936) which have received no treatment (Figs 8 27 30) On the other hand the impression has been gained that foci of necrosis and intense fibrosis are more common in the treated than in the untreated cases The appearances of this fibrosis closely resemble those seen in the more sclerotic varieties of the disease and Fox and Farley have suggested that the



FIG 1? 1
Area of dense collagen formation in a lymph node of Hodgkin s disease following heavy irradiation (H and E × 110)



FIG 12 2
Necrosis fibrosis and reticulin collapse following heavy irradiation in a case of Hodgkin s disease (H and E 110)

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FIG 1 3
Area of dense collagen formation in a lymph node of Hodgkin s disease following heavy irradiation (H and E × 110)



FIG 1? 4
Necrosis fibrosis and reticulin collapse following heavy irradiation in a case of Hodgkin s disease (H and E × 110)

changes following irradiation may be described as an accelerated natural course of events (Figs 12 1 and 12 2)

The effect of irradiation therapy on prognosis in the primary tumours of lymphoid tissue *has led to some difference of opinion* There are those (Barron 1926 O Brien 1941) who have maintained that there is no evidence that irradiation produces any lengthening of life but this view must be exceptional It is true that in the more anaplastic and rapidly advancing tumours the radiosensitivity is considerable so that large masses may be said to melt but the growth of new tumours elsewhere is equally rapid so that although local symptoms may be relieved dramatically lasting results are very rare In the case of Hodgkin s disease however occasional cases are seen where survival does seem to be prolonged considerably by irradiation and where at autopsy advanced fibrosis and hyalinisation in the lesions strongly suggests irradiation effect

A case illustrating this point may be quoted from the Westminster Hospital series where a male aged forty three years presenting with a mass in the *axilla a biopsy from which showed appearances typical of Hodgkin s disease* survived a period of eleven years and two months During the whole of this time clinical evidence of the disease was present and on two occasions once after six years and again *after nine years the patient* was moribund Irradiation therapy was given on numerous occasions with marked clinical improvement each time and until the terminal stages he was able to continue an active life At autopsy there was a small amount of serous fluid in the left chest and throughout both lungs were small well-circumscribed greyish deposits showing a small amount of yellow hard necrotic material in their centre (Fig 8 10) Enlarged glands were found in the left axilla mediastinum *coeliac and para aortic regions* and *in the latter area they formed a confluent* mass extending down to the bifurcation of the aorta The liver weighed fifty nine ounces and showed scattered yellowish deposits throughout its substance The spleen which was adherent to the left diaphragm showed a well circumscribed mass occupying the majority of its substance which on cut surface showed an appearance very similar to that seen in the smaller deposits in the lungs namely of greyish material peripherally with a central very hard zone of necrosis The left kidney showed two small deposits of a similar nature just under the capsule and apart from this there were no other abnormalities

The histological appearances showed in some areas a *picture of pleo* morphic cellular proliferation typical of Hodgkin s disease of an anaplastic type In many zones however the picture was one of intense fibrosis with hyalinisation together with areas of necrosis (Figs 12 3 and 12 4)

In a case of this type it is difficult to escape the conclusion that irradiation had played a considerable part in prolonging life At no time was there any question of the diagnosis being incorrect and for a case of Hodgkin s disease eleven years represents a very long survival In addition to this there is the

mustard is rapid and it remains active after intravenous injection only for a few minutes

By this and other tests they infer that the action of HN2 and X rays on malignant cells is fundamentally different and they criticise the use of the term radio mimetic as descriptive of the action of the nitrogen mustards pointing out that the use of such a term may obscure certain fundamental differences of action by overemphasising a series of morphological appearances which represent only the final change in a complicated process Certain derivatives of the nitrogen mustards of which R48 is the most important (Matthews 1950) together with other cytotoxic agents such as Tri-ethylene Melamine (T E M) the action of which has been described by Meyer *et al* (1951) Paterson and Boland (1951) Pillow (1951) and Willett *et al* (1951) have been used in the treatment of lymphoid tissue tumours but as yet their value can be regarded only as experimental

remarkable fact that on two occasions the patient was virtually moribund and even in a disease where remissions are well known recovery was striking unless one accepts the fact that the therapy was responsible Finally both the macroscopic and microscopic appearances at autopsy were so unlike those in a typical case of Hodgkin s disease as to make it seem certain that irradiation was responsible

To summarise therefore no doubt exists that irradiation can produce immediate effects of a dramatic nature and in the early stage of the disease may restore patients to normal activity for varying periods of time As regards evidence of increasing length of life *no conclusive data exist but* there is much to suggest that in a number of cases increased survival periods are achieved

Chemotherapy

Large numbers of drugs have been used over the years in the treatment of these conditions none of which can be said to have had any specific effects until the introduction of certain cytotoxic poisons of which β chlorethyl amines (nitrogen mustards) and sulphides have been used most commonly These drugs have been exhibited for the most part in the terminal stages of the diseases after irradiation has ceased to be effective and reports of their clinical effectiveness have been given by Rhoads (1946) and Zanes *et al* (1948) All authors are in agreement that only in Hodgkin s disease are any effects of lasting value obtained In a series of nineteen cases treated at Westminster Hospital among which nine were examples of Hodgkin s disease improvement was achieved in eight cases seven of which were in the Hodgkin s disease group The other case which showed some improvement was a case of reticulum cell sarcoma Four cases of anaplastic sarcoma and four cases of lymphosarcoma were unaffected (Allchin 1952)

Changes in the tissues following the use of nitrogen mustard have not shown any striking individual characteristics and autopsies performed personally on cases treated by this group of drugs have not revealed any particular features

For this reason many authors have spoken of the action of nitrogen mustards as being radio mimetic Koller and Casarini (1952) however working with methyl bis (β chlorethyl) amine or HN2 suggest that differences exist from the action of X rays on tumour cells as determined by experiments on the Walker carcinoma implanted in a rat

Their results show that the maximum number of injured malignant cells were found early after irradiation and later after treatment with *HN2*

The justification for making a time comparison of this sort depends on the fact that during irradiation ionisation takes place in the cell immediately (Lea 1946) setting up a reaction chain which leads to a definite biological phenomenon Similarly there is no substantial delay between administration of HN2 and its primary reaction in the organism Hydrolysis of nitrogen

picture at a particular stage of the disease must be attempted therefore and it has been found that in the series of cases reviewed here this has been possible It may be useful to make a personal observation at this point in order to stress that the vast majority of cases seen at Westminster Hospital have provided no great difficulty in their assessment Thus whilst it is of value to realise the problems of diagnosis which may exist the practical application has not been found to be overwhelmingly complicated

One might be tempted to suggest that only *three* different diseases exist in the group of primary tumours of lymphoid tissue—the lymphocytic variety the mixed cell variety and the reticulum cell variety

Further each one of these might be said to exhibit more chronic or well differentiated forms at one extreme and more acute or anaplastic types at the other with the average and most frequent types of clinico-pathological picture lying somewhere between the two

Carrying such an argument to its logical conclusion it would be justifiable to consider only three disease processes lymphosarcoma Hodgkin s disease and reticulum cell sarcoma and to recognise grades of malignancy in relation to histology and prognosis within each group

Such a concept is attractive and ultimately may well prove to be correct but in the light of our present knowledge it would certainly represent an oversimplification of the facts

At the present time therefore it seems wiser to retain the six subgroups which have been used in the preceding descriptions and which may be repeated here —

Follicular lymphoma Lymphosarcoma	Lymphocytic proliferation
Reticular lymphoma Hodgkin s disease	Mixed cell proliferation
Reticulum cell sarcoma	
Anaplastic sarcoma of lymphoid tissue	A group including the anaplastic variants of all types

(2) Presentation of the Disease

The symptoms associated with the primary tumours of lymphoid tissue have been for the most part of a general and somewhat vague nature Thus tiredness malaise pallor loss of weight and skin irritation have been the most frequent Physical signs at the time of presentation of the disease have usually been associated with enlargement of some area of lymphoid tissue By far the most frequent incidence is lymph node tumour formation particularly in the neck whilst mediastinal gland masses and a palpable spleen have also been important physical signs

Involvement of particular sites have led to specific syndromes such as the dyspnoea associated with mediastinal masses

CHAPTER 13

GENERAL CONCLUSIONS

IT is now proposed to make an attempt to sum up what are considered to be the main features which go to the analysis classification diagnosis and estimation of prognosis in primary tumours of lymphoid tissue based on what has already been said

The discussion will be grouped under the following headings —

(1) Uniformity of cellular origin and classification of morphological types
(2) Presentation of the disease
(3) Frequency age incidence and prognosis
(4) Diagnostic methods and differential diagnosis

(1) Uniformity of Cellular Origin

The foregoing descriptions of tumour types have indicated that specific varieties exist and whilst it is true to say that the vast majority of cases seen in this series fall easily into one of the described groups yet any individual case may be difficult to place from one of two points of view (Figs 3 1 3 2)

Firstly its histological picture may not conform exactly to one of the described types and secondly it may change in appearance as the disease progresses

The first problem is usually very closely linked with the second for example it may not be easy in all cases to decide whether to place a particular example in the group of reticular lymphoma or Hodgkin s disease Again the differentiation between an anaplastic sarcoma and a cellular Hodgkin s disease or between a follicular lymphoma and lymphosarcoma may cause confusion

It is clear however that if one accepts the theory of origin from a common parent cell and realises the possible progression of the better differentiated varieties into more anaplastic forms as the disease advances then such difficulties are inevitable and classification as in all diseases will be to some extent arbitrary

For this reason some authors (Custer and Bernhard 1948) have suggested that such fluidity in histological pattern exists between the various types that any rigid classification of lymphatic tumours is artificial and confusing

This is an extreme view and it is considered of the utmost value to retain the subgroups suggested here if for no other reason than as a method of assessing prognosis In the majority of cases only one biopsy is available in any individual example and if further material is seen later in the disease it may be difficult to assess the effect of irradiation or other complicating features Some generalisation of prognosis based on the clinico pathological

Once the question of leukaemia has been decided the chief differential diagnostic problem will be to distinguish those conditions which cause lymph node enlargement other than primary tumours of lymphoid tissue These have been discussed already in detail but one point may be stressed again here It is a basic truth that primary tumours inasmuch as they are arising intrinsically will replace normal architecture by their own growth whilst the vast majority of other conditions—inflammation lipoidoses sarcoidosis metastatic neoplasms—will proliferate primarily in the sinuses and compress or infiltrate the surrounding normal lymphoid tissue It is considered that the differentiation between this sinus proliferation displacing essentially normal tissue and a primary abnormality of lymphoid tissue replacing normal architecture *is perhaps the most important single feature to be decided in* assessing a lymph node biopsy It must also be stressed that the reticulum cells lining sinuses may proliferate and become very much larger than normal as a result of inflammatory stimulation On occasion binucleated forms may be seen of the type usually known as Sternberg Reed cells so that the demonstration of an isolated Sternberg Reed cell does not necessarily indicate a diagnosis of Hodgkin s disease

In that lymphoid tissue reacts by cellular proliferation to a large number of conditions both in health and disease it is important when examining a lymph node biopsy that an apparent abnormality should not be diagnosed lightly as ? Hodgkin s disease a label far too readily applied and one which leads to many complications both for the patient and also when an attempt is made to analyse the frequency and prognosis of tumours of lymphoid tissue

Distinction between the varieties of tumours of lymphoid tissue has not usually been possible on physical examination alone although certain helpful factors may be mentioned Thus the lymph node masses in Hodgkin s disease are usually smaller than those in lymphosarcoma Rapid clinical progression of the disease is quickly apparent in the more malignant variants whilst multiplicity of symptomatology has been usual in the rapidly advancing tumours as opposed to a single complaint in the more benign varieties (Tables 6 8 10 12 15 17)

(3) Frequency, Age Incidence and Prognosis

Hodgkin s disease accounts for very nearly 50 per cent of the primary tumours of lymphoid tissue whilst lymphosarcoma and the anaplastic tumours between them make up roughly 40 per cent of the remainder (Table 1) The histological differentiation between these three tumour types does not present any great difficulty The three remaining named types include one which is rapidly malignant (reticulum cell sarcoma) and two which are the most benign of the whole group (follicular lymphoma and reticular lymphoma)

The age incidence (Table 3) of these diseases shows certain differences thus Hodgkin s disease and reticular lymphoma occur typically in young adults (twenty to forty years) lymphosarcoma and follicular lymphoma show an increasing frequency with advancing age but lymphosarcoma may affect an important group under twenty years whilst the anaplastic sarcomas are tumours of those over forty five to fifty years of age

The prognosis of the six named varieties of tumours show certain well marked differences—follicular lymphoma and reticular lymphoma are of relatively benign potentiality Hodgkin s disease occupies a middle position of moderate malignancy as compared with others in the group lymphosarcoma shows a difference according to age of incidence acting in an intensely malignant fashion in young people whilst its prognosis is only slightly worse than Hodgkin s disease in the older age groups reticulum cell sarcoma and the anaplastic sarcomas are malignant and rapid in their downhill course (Table 2)

(4) Diagnosis and Differential Diagnosis

Apart from the general clinical features already mentioned the diagnosis of primary tumours of lymphoid tissue depends almost entirely on a biopsy—usually from a lymph node—together with a knowledge of the state of the peripheral blood as obtained either by a simple blood count or by an examination of the bone marrow This latter knowledge will serve to differentiate the leukaemias from the tumours and it must be remembered that repeated blood counts are of importance as leukaemic blood pictures may develop during the course of the disease

The general features of lymph node biopsy have been fully discussed and it is only necessary to stress the importance of obtaining an intact gland together with some surrounding connective tissue if possible from a group not usually the site of inflammatory changes Adequate and rapid fixation is essential so that architecture or the destruction thereof can be studied carefully

follicular patternwork of cells of lymphoblast type showing pleomorphism and numerous mitoses

In hospital she pursued a downhill course and died At post mortem multiple lymph node masses were found in the abdomen axillae and inguinal groups The spleen and liver were enlarged and infiltrated Histology revealed a picture very similar to that seen at biopsy namely a follicular pattern of predominately lymphoblast type in the malignant phase

This patient followed an extremely rapid course living only one year from the time when she was first seen In view of the remnants of a follicular pattern seen histologically together with the fact that the main mass of lymph nodes involved by disease were situated in the abdomen it is interesting to speculate whether the tumour process had been present in a more benign form for a considerable time before the patient became aware of any abnormality

Case No 3

Female aged sixty four years presented in December 1950 with enlarged glands in neck axillae and groins which had been present for two years She remained quite well until March 1951 when her spleen became palpable and a biopsy from her cervical glands showed the histological picture of follicular lymphoma In February 1952 her spleen had become larger and it was removed Histological appearances in the spleen were similar to those found in the lymph nodes She remained well after the operation with two fingers breadth hepatomegaly and when last seen in October 1952 was quite fit At no time has there been any abnormality of the peripheral blood

Only four years have elapsed since she first noticed enlarged glands but the case is described as the surgical removal of the spleen afforded an opportunity for its careful examination (Figs 5 1 5 2)

Case No 4

Male aged fifty four years was first seen in September 1949 with a very large ulcerating cauliflower like growth destroying the right tonsil In addition several large rubbery glands were palpable in the upper deep cervical group on the right side No other abnormalities were detected at this time

A biopsy was performed on the tonsillar mass which showed replacement of normal architecture by sheets of well formed lymphocytes The blood count showed a normal cell distribution and a diagnosis of lymphosarcoma was made

Irradiation therapy resulted in complete healing of the lesion (Figs 6 18 6 19)

In March 1950 palpable nodes appeared in both axillae which disappeared following irradiation therapy In November 1950 a mass in the left infraclavicular fossa and in May 1951 another in the left buttock was dispersed by irradiation whilst in October 1951 infiltration of the twelfth thoracic vertebra was discovered

In December 1951 the liver became palpable for the first time together with a large intra abdominal mass of para aortic glands The patient pursued a rapidly downhill course dying in January 1952 two years and three months after the onset of symptoms The tonsillar area remained clinically free of disease until the time of death At autopsy no remaining disease was found in the tonsillar area but there was widespread involvement of other organs including liver spleen lungs and numerous lymph nodes

CHAPTER 14

ILLUSTRATIVE CASES

Follicular Lymphoma

1	Male	Aged 44 years	Typical case 9½ years survival Fit and well
2	Female	Aged 53 years	Rapid passage into malignant phase
3	Female	Aged 64 years	Splenectomy performed

Lymphosarcoma

4	Male	Aged 54 years	Typical case 2 years 3 months survival
5	Male	Aged 28 years	*Rapid death with mediastinal involvement*
6	Male	Aged 56 years	Involvement of ileum only
7	Male	Aged 7 years	Leukosarcoma

Reticular Lymphoma

8	Male	Aged 18 years	19½ years survival with onset of malignant phase after 15 years
9	Male	Aged 33 years	11 years survival

Hodgkin's Disease

10	Male	Aged 33 years	Typical case 5½ years survival
11	Female	Aged 19 years	One organ only involved—the lung
12	*Female*	*Aged 28 years*	*Progression into anaplasia*
13	Male	Aged 33 years	Progression into anaplasia and ulceration following irradiation
14	Male	Aged [illegible]3 years	Association with tuberculosis

Reticulum Cell Sarcoma

15	Male	Aged 60 years	Typical 12 months survival
16	Female	Aged 62 years	Primary onset in bone 17 months survival

Anaplastic Sarcoma of Lymphoid Tissue

17	Female	Aged 50 years	Long survival after isolated lesion removal Alive and well after 6½ years
18	Male	Aged 37 years	Rapid terminal course with long clinical history
19	Male	Aged 52 years	Typical rapid course 6 months survival

Case No 1

Male aged forty four years was first seen in October 1943 complaining of a lump in the neck which had been present for three months Several glands were palpable in the neck as well as in both axillae and inguinal regions A biopsy showed a histological picture of follicular lymphoma with well marked follicular formation Irradiation therapy was given to the neck axillae and groins and the lymph nodes became very much smaller He returned to work and has remained quite fit until the present time nine and a half years after his original illness There has been no hepatosplenomegaly or abnormality in the peripheral blood at any time

Case No 2

Female aged fifty three years complained of weakness and lethargy in September 1947 and on examination an abdominal mass and an enlarged spleen were found Biopsy from the abdominal glands in November 1947 revealed a

by sheets of mature lymphocytes together with numerous groups of lymphocytes lying free in the sinuses (Fig 6 16)

LEUCOCYTE COUNTS

26th December 1947	4 096 per cu mm	24% lymphocytes
25th February 1948	4 100 per cu mm	60% lymphocytes
8th March 1948	130 000 per cu mm	100 % atypical lymphocytes

The child pursued a downhill course despite high voltage X ray therapy and died on 27th March 1948 five months after the commencement of the disease and two months after the first evidence of leukaemia

At post mortem infiltration of many organs by cells of mature lymphocyte type was found a point of some interest being the unusual finding of invasion of the right testicle Cause of death was aspiration of blood from many bleeding points around the nasopharynx

Case No 8

Male aged eighteen years was first seen in February 1933 with a mass in the neck General health was unimpaired but a biopsy when reviewed revealed the appearances of reticular lymphoma High voltage X ray therapy was given and the gland mass disappeared leaving the patient in good health until March 1947 when he noticed an enlargement of a cervical gland which had been palpable for several years In September 1948 a second biopsy was performed and the histo logical appearances showed considerable change from those seen originally There was a pleomorphic cellular pattern of predominately lymphoblastic type Irradiation was given to the neck with diminution in size of the glands but in April 1949 the patient returned complaining of ill health for the first time and a gland mass was discovered in the epigastrium displacing the stomach and duodenum Irradiation to the abdomen was followed by considerable improvement and a return to normal health until February 1950 when the appearance of a mediastinal mass caused dyspnoea Irradiation to this area was followed by improvement of symptoms and in May 1951 following a period of pain in the back a deposit was discovered in the eleventh thoracic vertebra About this time skin nodules appeared over the chest and abdomen and in June 1951 a mass became palpable in the left buttock During the next year the patient developed a slowly advancing anaemia with progressive weakness and malaise and he died in April 1952 with multiple deposits in the lymph nodes lungs and marrow The total duration of the disease from the onset of the first lesion was nineteen years with a period of approximately fifteen years elapsing between the first biopsy and the onset of advancing malignancy (Figs 7 12 15)

Case No 9

Male aged thirty three years was first seen in April 1939 when a gland was removed from the left side of the neck which showed the histological appearance of reticular lymphoma No therapy was given and the patient remained well until April 1944 when there was a recurrence of enlarged glands in the right side of the neck A second biopsy in May 1944 again showed a histological picture of reticular lymphoma Irradiation therapy was followed by regression of the gland mass In July 1946 and February 1947 lymph nodes were again palpable in the neck

Case No 5

Male aged twenty eight years was first seen in May 1949 complaining of stiffness of the neck with swelling and hoarseness A biopsy of a gland in the neck was performed which showed sinus catarrh only The patient was admitted with superior vena caval obstruction and radiographs revealed a large mass of cervical and mediastinal glands producing the obstruction Irradiation therapy was given followed by complete regression of the cervical and mediastinal masses In August 1949 there was a return of dyspnoea and superior vena caval obstruction together with distension of the abdomen Nitrogen mustard therapy was given with little relief and the patient died on the 22nd September four months after the onset of his first symptom

At post mortem it was found that the patient had died as the result of a pulmonary embolus in the presence of a massive left sided pleural effusion Enlarged lymph nodes were found in the upper cervical region on both sides in the mediastinum where they were producing a large mass obstructing the superior vena cava and in the para aortic region The liver and spleen were both enlarged and contained pale irregular masses scattered through their substance Histology of all abnormal areas revealed sheets of typical lymphocytes At no time during life had there been any abnormality of the peripheral blood

The interest of this case lies in the fact that a lymph node removed at the commencement of disease revealed no evidence of lymphosarcoma despite the extreme rapidity of progression of the disease

Case No 6

Male aged fifty six years was first seen in April 1946 suffering from chronic intestinal obstruction Twenty one centimetres of terminal ileum were resected and the specimen showed a localised area of narrowing caused by diffuse lymphocytic infiltration of the bowel wall (Figs 6 3 6 4) Enlarged glands appeared in the left axilla and right groin in September 1946 but these disappeared following irradiation therapy and the patient was fit until January 1948 when a barium meal revealed obstruction at the splenic flexure In March 1948 a colostomy was performed but the patient pursued a rapidly downhill course and died three days later

At post mortem careful examination revealed no evidence of existing lympho sarcoma The obstruction in the splenic flexure was a small annular carcinoma with no evidence of any metastasis The cause of death was paralytic ileus following the operation and it must be assumed in this case that the lymphosarcoma had been eliminated completely and that the carcinoma of the colon was a dissociated condition

Case No 7

Male aged seven years was admitted to hospital on 13th October 1947 with collapse of the left upper lobe caused by enlarged mediastinal and bronchial glands Small doses of high voltage X rays resulted in disapparance of the mass and re aeration of the lung A blood count at this time was normal

On 1st February 1948 low back pain commenced and a mass was found overlying the right mandible The liver was enlarged as was the right testicle Biopsy of a cervical gland at this time showed replacement of normal architecture

by sheets of mature lymphocytes together with numerous groups of lymphocytes lying free in the sinuses (Fig 6 16)

LEUCOCYTE COUNTS

26th December 1947	4 096 per cu mm	24% lymphocytes
25th February 1948	4 100 per cu mm	60% lymphocytes
8th March 1948	130 000 per cu mm	100% atypical lymphocytes

The child pursued a downhill course despite high voltage X ray therapy and died on 27th March 1948 five months after the commencement of the disease and two months after the first evidence of leukaemia

At post mortem infiltration of many organs by cells of mature lymphocyte type was found a point of some interest being the unusual finding of invasion of the right testicle Cause of death was aspiration of blood from many bleeding points around the nasopharynx

Case No 8

Male aged eighteen years was first seen in February 1933 with a mass in the neck General health was unimpaired but a biopsy when reviewed revealed the appearances of reticular lymphoma High voltage X ray therapy was given and the gland mass disappeared leaving the patient in good health until March 1947 when he noticed an enlargement of a cervical gland which had been palpable for several years In September 1948 a second biopsy was performed and the histological appearances showed considerable change from those seen originally There was a pleomorphic cellular pattern of predominately lymphoblastic type Irradiation was given to the neck with diminution in size of the glands but in April 1949 the patient returned complaining of ill health for the first time and a gland mass was discovered in the epigastrium displacing the stomach and duodenum Irradiation to the abdomen was followed by considerable improvement and a return to normal health until February 1950 when the appearance of a mediastinal mass caused dyspnoea Irradiation to this area was followed by improvement of symptoms and in May 1951 following a period of pain in the back a deposit was discovered in the eleventh thoracic vertebra About this time skin nodules appeared over the chest and abdomen and in June 1951 a mass became palpable in the left buttock During the next year the patient developed a slowly advancing anaemia with progressive weakness and malaise and he died in April 1952 with multiple deposits in the lymph nodes lungs and marrow The total duration of the disease from the onset of the first lesion was nineteen years with a period of approximately fifteen years elapsing between the first biopsy and the onset of advancing malignancy (Figs 7 12 15)

Case No 9

Male aged thirty three years was first seen in April 1939 when a gland was removed from the left side of the neck which showed the histological appearance of reticular lymphoma No therapy was given and the patient remained well until April 1944 when there was a recurrence of enlarged glands in the right side of the neck A second biopsy in May 1944 again showed a histological picture of reticular lymphoma Irradiation therapy was followed by regression of the gland mass In July 1946 and February 1947 lymph nodes were again palpable in the neck

and disappeared on each occasion following irradiation In July 1949 the patient developed cough and dyspnoea associated with glands in the mediastinum Small lymph nodes were palpable in the neck axillae and inguinal regions and the liver was palpable two finger breadths below the costal margin At this time the patient developed symptoms of general ill health for the first time and despite treatment with nitrogen mustard developed progressive anaemia and died in March 1950 eleven years after the onset of the first symptom

Case No 10

Male aged thirty three years first noticed a lump in the left side of the neck in April 1946 In September 1946 further swellings appeared in the left side of the neck and the left axilla A biopsy showed appearances typical of Hodgkin s disease The glands disappeared and the patient returned to full duty following irradiation He remained fit until November 1950 when a large mass of glands appeared in the left axilla and in the left supraclavicular region Radiographs of the chest and spine were normal the blood count was normal and there was no enlargement of the liver or spleen Nitrogen mustard therapy was used at this time All the enlarged glands diminished in size and the general condition of the patient improved In December 1950 the patient commenced to have an irregular fever of Pel Ebstein type and the liver was enlarged two finger breadths below the costal margin A liver aspiration biopsy performed in March 1951 showed an infiltration of the liver substance typical of Hodgkin s disease In May 1951 the patient had become anaemic and at about this time skin nodules appeared in the neck and chest From this point onwards the patient pursued a downhill course with progressive anaemia and died with massive right pleural effusion and bronchopneumonia in September 1951 five and a half years after the onset of the disease

At post mortem in addition to the pleural effusion and pneumonia already described enlarged lymph nodes were found in the left side of the neck in the mediastinum and in the para aortic region Other organs involved included both lungs the liver and spleen right kidney and the bone marrow in the sternum and right femur Histological examination of all the invaded areas showed an *appearance typical of Hodgkin s disease*

Case No 11

Female aged nineteen years was first seen in April 1941 A large mass was *discovered in the left lung region High voltage X ray treatment was given in* several courses until June 1945 The patient died in December 1946 five and a half years after the original discovery of the mass in the chest and at post mortem no abnormalities were found anywhere other than the lungs where there was a large mass arising in the lower lobe of the left lung and occupying the entire left pleural space with penetration of the diaphragm to compress the left kidney The cause of death was a diffuse bronchopneumonia in the contralateral lung but a small area of infiltration 1 cm in diameter was found at the base of the lower lobe on the right side Histology from the main tumour mass and from the nodule in the right lung showed appearances typical of Hodgkin s disease (Fig 8 9)

Case No 12

Female aged 28 years was first seen in March 1939 when she complained of a swelling in the neck Biopsy of enlarged lymph nodes in this region showed appearances typical of Hodgkin s disease She was given deep X ray treatment, and in September 1941 passed A 1 into one of the Services Between 1941 and her death in March 1946 seven years after her first illness various enlarged glands appeared including a mass in the left breast which was treated by high voltage X rays and disappeared At post mortem enlarged glands were found in the right neck mediastinum and abdomen Invasion of the liver and stomach had occurred and the splenic artery had been eroded There was a mass in the thorax involving the pericardium and invading the lungs The cause of death was haemorrhage from the splenic artery Microscopy of the lymph nodes and invaded organs taken at autopsy showed a completely anaplastic picture quite unlike that seen in the original biopsy (Figs 8 33 37)

Case No 13

Male aged thirty three years first noticed a swelling in the left supraclavicular region in October 1948 In January 1949 a gland biopsy revealed the appearances of Hodgkin s disease (Figs 10 15 17) At this time enlarged glands were present on both sides of the neck in the right axilla and the superior mediastinum Irradiation therapy was given to the neck and the right axilla in February and again in March In May a gland became palpable in the left axilla together with swelling in the anterior part of the chest wall These areas were also treated with irradiation The patient remained well until March 1951 when a discharging sinus appeared in the region of the biopsy scar in the right supraclavicular area Examination of smears from this discharge showed only degenerating pus cells Radiographs taken of the chest showed no evidence of any intrathoracic abnormalities but there was an extensive irregular periostitis of the right clavicle together with some destruction of the anterior part of the sternum by the overlying soft tissue mass Further irradiation therapy was given in May and June 1951 but the discharging sinus remained (Fig 10 12) The patient was then treated with R48 but ulceration in the right supraclavicular region progressed to form two deep craters and at this time the patient was suffering from considerable pain (Fig 10 13) In November 1951 a biopsy taken from the edge of the ulcer showed an extremely cellular mass made up of a pleomorphic cellular proliferation including numerous reticulum cells of Sternberg Reed type together with many giant cells undergoing mitosis There was also considerable necrosis in the area and it was considered that the degree of anaplasia had advanced sufficiently to merit the title of anaplastic sarcoma of lymphoid tissue (Figs 10 18 20) Treatment with nitrogen mustard was attempted at this time but the ulcer cavity continued to extend and the two cavities were at this time (December 1951) almost continuous with a bridge of skin running between them The clavicle was almost entirely replaced by tumour substance The peripheral blood count was normal The sternal marrow picture was normal and the liver and spleen were not palpable During the following six months the patient pursued a slowly downhill course with increasing anaemia and died in August 1952 a period of three years and ten months from the onset of disease

The post mortem was performed by Dr E Neumark at St Mary s Hospital London to whom I am indebted for the following summary of his findings

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The ulcer crater in the right supraclavicular area had increased enormously baring the right clavicue and extending to the right sterno clavicular joint (Fig 10 14) Over the right chest there were numerous nodules of tumour infiltration The hilar glands were invaded and both lungs showed irregular nodules of tumour There was a large tumour mass at the right side of the parietal pericardium and a large right pleural effusion with nodularity of the right parietal pleura The liver and spleen were congested but otherwise normal and there were no abnormalities of the cells in the marrow of the femur

The interest of this case lies in the large ulcerating lesion produced in association with the biopsy scar and it must be assumed that it represents partly an active tumour proliferation and partly a weakening in the area following irradiation This case also shows the progression of anaplasia with the advance of the disease (Figs 10 15 20)

Case No 14

Male aged twenty three years noticed a lump in the right side of the neck in 1945 A biopsy showed the appearances of Hodgkin s disease Irradiation therapy was given during 1946 47 to the neck mediastinum axillae right supraclavicular fossa and left groin with regression of the lumps which appeared in these areas following each course of treatment In June 1947 the patient was admitted complaining of dyspnoea tiredness and pain in the neck and chest Glands were palpable in the right supraclavicular and left inguinal regions There was a mass in the left iliac fossa and an X ray of the chest showed extensive infiltration of both lungs A biopsy taken from one of the lymph nodes in the inguinal region revealed a histological picture of Hodgkin s disease Nitrogen mustard therapy was used with diminution of size of most of the glands but severe anaemia and leucopenia developed in August 1947 Dyspnoea and cough became very trouble some and an X ray of the chest revealed increased infiltration of the left upper lobe with evidence of cavitation Examination of the sputum revealed tubercle bacilli in several specimens The patient pursued a downhill course with advancing cavitation in the lungs but no further enlargement of lymph nodes and died in May 1948 three years after the onset of the disease

Post mortem revealed extensive tuberculous infiltration of the lungs and many other organs including kidneys liver and spleen In several lymph nodes as well as in the liver a mixture of the appearances of Hodgkin s disease with those of tuberculosis could be demonstrated (Fig 8 11)

Case No 15

Male aged sixty years first complained in September 1946 of loss of weight and general ill health Enlarged glands were found in the left neck and groin There was some anaemia Despite irradiation therapy further masses appeared in the abdomen and neck A steadily downhill course ensued and death occurred in November 1947 just one year after the first abnormalities were noted Histology from the gland masses showed a proliferation of large cells with well-defined nuclei and eosinophilic nucleoli typical of the appearances of reticulum cells (Fig 9 2)

Case No 16

Female aged sixty two years complained of a lump arising from the left clavicle in September 1948 A biopsy showed sheets of reticulum cells proliferating in a scanty stroma Irradiation was given but in June 1949 a destructive lesion was discovered in the left tibia and in September 1949 a lesion was found in the right ulna At this time an ulcerative lesion of the tonsil developed a biopsy from which showed a proliferation of reticulum cells in uniform masses In November a generalised lymphadenopathy developed involving both sides of the neck axillae and groins In December 1949 despite irradiation therapy a pathological fracture of the *left tibia occurred R48 was given at this time by mouth but the patient* pursued a downhill course and died in February 1950 seventeen months after the onset of disease At autopsy a widespread bronchopneumonia was the cause of death and diffuse lymphadenopathy and bony involvement including both tibias right ulna and left clavicle was discovered A careful search revealed no evidence of any primary malignant tumour anywhere and the histological picture of all the affected areas was of sheets of typical reticulum cells proliferating in a scanty stroma

Case No 17

Female aged fifty years was first seen in April 1946 when she complained of lumps in the neck which had been present for three weeks She was admitted to hospital and examination revealed large discrete firm glands in the right supraclavicular fossa There had been a loss of weight of about eight pounds during the preceding few months but otherwise she was symptomless with no other abnormal physical signs

A biopsy was performed at which the affected lymph nodes were removed which revealed replacement of normal architecture by a grossly anaplastic pleomorphic cellular proliferation including numerous giant cells and mitoses A diagnosis of anaplastic sarcoma of lymphoid tissue was made and irradiation therapy was given to the supraclavicular area Since this time she has remained well with no evidence of enlarged glands at any time and has received no further treatment When last seen in September 1952 she was clinically free from disease six years and four months after the onset of disease

Case No 18

Male aged thirty seven years had a sudden onset of abdominal pain in June 1947 and at this time enlarged cervical glands were noticed to increase in size although the patient had been aware of their presence for several years A large abdominal mass was discovered and a biopsy of a gland from the left supraclavicular fos a showed a highly pleomorphic picture with numerous giant cells mitoses and small areas of *necrosis A diagnosis of anaplastic sarcoma of lymphoid tissue* was made Nitrogen mustard therapy was given as in addition to the cervical and abdominal masses there were enlarged glands in the axillae as well as hepato splenomegaly There was no improvement in general condition following treatment although the glands became somewhat smaller Following a period of steady deterioration the patient died four months after his first complaint although as has been stated above enlarged cervical glands had been present for several years

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This is an example of a case which pursued a very short course from the time of first diagnosis to death It is however difficult to be certain that this period represents the whole course of the disease It would appear possible that a longer period of subclinical affection preceded the final exacerbation

Case No 19

Male aged fifty two years first noticed lumps in the neck in December 1941 A gland removed for biopsy showed complete replacement of normal architecture by pleomorphic cells including giant varieties and many undergoing mitosis A diagnosis of anaplastic sarcoma of lymphoid tissue was made On examination enlarged glands were found in both sides of the neck both axillae and both inguinal regions The patient complained of breathlessness and had a cough Irradiation therapy was given with little result and in June 1942 six months after the onset of the disease he died

At post mortem the body was emaciated and gland masses were found on both sides of the neck in both axillae in the mediastinum in the para aortic region and in both inguinal fossae There was a large right pleural effusion with collapse of the right lung The spleen and both kidneys were infiltrated by tumour substance Bone marrow examination in the sternum and right femur showed numerous tumour deposits Careful search revealed no evidence of any primary neoplastic process

Histological examination of the involved areas showed an essentially similar appearance throughout with replacement of normal architecture by masses of ana plastic cells with scattered areas of necrosis

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